Healthcare Utilization in Rheumatic Diseases

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ABSTRACT

Rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA) and axial spondyloarthritis (AxSpA; including ankylosing spondylitis) are inflammatory rheumatic diseases contributing to a substantial burden on both the patient and society. During the past couple of decades, active treatment strategies and pharmacological advancements have altered their cost structures, with scarce data existing on modern cohorts. Particularly for JIA in adulthood, the cost outcomes and clinical outcomes remain poorly documented. For these four rheumatic diseases, we set out to explore the health service-related costs, with emphasis on both costs of the index rheumatic disease and the costs of comorbidities. We investigated unmet needs by identifying disease-related factors attributable to distinct healthcare utilization patterns.

We linked two population-based databases: a longitudinal clinical dataset with high diagnostic validity from the Jyväskylä Central Hospital rheumatology unit, and administrative data covering all public healthcare in the area. Collection of the clinical data took place between May 2007 and March 2016, and health service-related costs in euros (€) were available for fiscal year 2014. We studied the clinical outcomes in 218 adult JIA patients, with health service-related costs available for 119 adult patients with JIA, 213 with PsA, 1086 with RA, and 277 with AxSpA. We compared their cost distributions and high healthcare utilization patterns.

Despite being heterogeneous, particularly regarding age, JIA, RA, PsA, and AxSpA shared similar patterns of healthcare resource utilization, both in terms of costs incurred by the rheumatic disease and by comorbidities. The majority of patients are doing overall well both in terms of patient-reported outcomes and health service-related costs, reflecting the effects of modern anti-rheumatic treatment. However, a tenth was recognizable as high healthcare utilizers (for JIA, 15%). Particularly pain, fatigue and disability, but also comorbidity and disease activity emerged as key factors affecting healthcare resource utilization. For all diseases, comorbidities accounted for two thirds of the total costs.

This study supports the existing evidence that active treatment of rheumatic diseases has entailed good outcomes and low healthcare resource utilization for the majority. Particularly chronic pain, fatigue, and disability seem to be important areas needing attention in treatment of rheumatic diseases.

TIIVISTELMÄ

Nivelreuma, nivelpsoriaasi, lastenreuma ja selkärankareuma lukeutuvat tulehduksellisiin reumasairauksiin, jotka voivat aiheuttaa merkittävää haittaa potilaiden terveydelle ja elämänlaadulle. Viimeisten vuosikymmenten aikana tapahtuneet kehitysaskeleet hoitoperiaatteissa ja lääkehoidossa ovat parantaneet sairausennustetta mutta samalla lisänneet lääkehoidon kustannuksia. Näiden potilaiden terveyspalvelujen käytön kustannuksista on kuitenkin niukasti nykyaikaista tutkimustietoa.

Väitöskirjatutkimuksessa tarkasteltiin ja verrattiin näiden neljän tärkeän reumasairauden terveyspalvelujen käytön kustannuksia yhdistämällä kahdenlaisia rekisteritietoja: Keski-Suomen sairaanhoitopiirin potilastietojärjestelmän tietoja (GoTreatIT-monitorointi) reumasairauksia sairastavista potilaista vuosilta 2007-2016 ja euromääräisiä hoitotuotantotietoja perustuen terveydenhuollon hoitoilmoitusjärjestelmään, eli terveydenhuollon yhteydenottoihin ja käynteihin vuodelta 2014.

Ensimmäisessä osatyössä tarkasteltiin 218 potilasta, joilla oli lapsuusiässä alkanut reumasairaus, n.s. lastenreuma. Tärkein havaintomme oli, että tarkasteluaikana 16-30-vuotiaista lastenreumaa sairastavista valtaosalla toimintakyky oli hyvä ja erittäin harvalla havaittiin työkyvyttömyyttä. Toisessa osatyössä tarkastelimme 119 aikuista lastenreumaa, 213 nivelpsoriaasia, 1086 nivelreumaa ja 277 selkärankareumaa sairastavaa potilasta. Heidän keskimääräiset palveluidenkäyttökustannuksensa olivat varsin samanlaiset ja noin yksi kymmenestä potilaasta tunnistettiin terveyspalvelujen suurkäyttäjäksi. Selkärankareumaa ja lastenreumaa sairastavat olivat keskimäärin selvästi nuorempia kuin nivelreuma- ja nivelpsoriaasipotilaat ja heidän elinaikainen kustannuskertymänsä voidaan siten olettaa suuremmaksi. Kaksi kolmasosaa terveyspalvelujen käytöstä johtui liitännäissairauksista ja etenkin suurkäyttäjillä liitännäissairauksista johtuva kustannustaakka oli merkittävä. Liitännäissairauksien lisäksi terveyspalvelujen käyttöön vaikuttivat kipu ja alentunut toimintakyky. Kolmannessa osatyössä havaittiin ryhmittelyanalyysin keinoin keskeisimmäksi hoidon kehittämistarpeeksi krooninen kipu: noin kolmasosa nivelreumapotilaista koki kroonista kipua ilman merkittävää tulehdusaktiivisuutta.

Tutkimuksessa havaittiin, että terveyspalvelujen kustannustaakka oli tutkituissa reumasairauksissa varsin samankaltainen ja suurimmalla osalla potilaista terveyspalvelujen käyttöön liittyvät kustannukset ovat matalat. Pieni osa potilaista käyttää suurimman osan reumapotilaiden terveydenhuollon kokonaiskustannuksista. Tulehduksen rauhoittamisen lisäksi näiden potilaiden kohdalla tulee kiinnittää huomiota etenkin kivunhallintaan.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I. Mars NJ, Kerola AM, Kauppi MJ, Pirinen M, Elonheimo O, Sokka-Isler T. Healthcare costs and outcomes in adult patients with juvenile idiopathic arthritis: a population-based study. Scand J Rheumatol 2019;48(2):114-120.

II. Mars NJ, Kerola AM, Kauppi MJ, Pirinen M, Elonheimo O, Sokka-Isler T. Patients with rheumatic diseases share similar patterns of healthcare resource utilization. Scand J Rheumatol 2019. Epub ahead of print.

III. Mars NJ, Kerola AM, Kauppi MJ, Pirinen M, Elonheimo O, Sokka-Isler T. Cluster analysis identifies unmet healthcare needs among patients with rheumatoid arthritis. Submitted.

The original publications are referred to in the text by their roman numerals.

ABBREVIATIONS

AS	Ankylosing spondylitis
ACPA	Anti-citrullinated peptide antibodies
AxSpA	Axial spondyloarthritis
bDMARD	Biological disease-modifying anti-rheumatic drug
BMI	Body mass index
CI	Confidence interval
CHD	Coronary heart disease
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
CVD	Cardiovascular disease
DAS28	Disease activity score based on 28 joints
DRG	Diagosis-related group
ESR	Erythrocyte sedimentation rate
GLM	Generalized linear model
HAQ	Health assessment questionnaire
HLA	Human leukocyte antigen
ICD-10	International classification of diseases, 10th revision
ICPC2	International classification of primary care, second edition
IQR	Interquartile range
JCH	Jyväskylä Central Hospital
JIA	Juvenile idiopathic arthritis
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PCA	Principal component analysis
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SD	Standard deviation
SpA	Spondyloarthritis and spondyloarthropathy
tsDMARD	Targeted synthetic DMARDs
VAS	Visual analogue scale

1. INTRODUCTION

Infammatory rheumatic diseases cause a substantial burden to both the patient and to society.[1-3] Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease, and it is from an economical perspective the best studied rheumatic disease. Psoriatic arthritis (PsA), axial spondyloarthritis (AxSpA), and juvenile idiopathic arthritis (JIA) are other rheumatic disease entities involving inflammation in joints and impacting functional ability – but still, compared to RA, their economic consequences are less studied.

During recent decades, treatment strategies have evolved to render remission or low disease activity the main goal for RA, and also to an increasing extent for JIA, psoriatic arthritis, and potentially other inflammatory rheumatic diseases.[4-5] Effective treatment strategies have translated into more favorable outcomes and into changes in health-service needs and associated costs, particularly after biological disease-modifying anti-rheumatic drugs (bDMARDs) entered the market.[6-8]

JIA is diagnosed in childhood, and for some, the disease continues into adulthood. Only adult patients were studied in this thesis. If inflammation due to JIA has permanently affected the joints or the inflammation persists in adulthood, decades of living with the disease lead to high cumulative costs of healthcare resource utilization when compared, for instance, to rheumatoid arthritis, which has an age of onset much later in life. To prevent joint damage, children and adolescents with JIA are aggressively treated, but in the era of biologics, both cost outcomes and clinical outcomes in adult patients with JIA remain poorly documented.

In addition to their index rheumatic disease, many patients carry other morbidities. Multimorbidity, with many existing definitions, refers to the disease burden of multiple concurrent diseases, while comorbidity generally refers a specific disease in addition to the index disease. This thesis does occasionally use the terms interchangeably. Although the burden of comorbidites in inflammatory rheumatic diseases is well recognized, their costs are often overlooked.

With improvements in health status, there arises a need for updated research on current cost drivers, both in terms of disease characteristics and multimorbidities. This thesis falls under the category of cost-of-illness studies. More specifically, it assesses healthcare utilization, which refers to patient use of healthcare services, and

aims to improve upon prior research on the economic burden and cost drivers in adult patients with RA, PsA, AxSpA (including ankylosing spondylitis, AS), or JIA.

2. REVIEW OF THE LITERATURE

This review begins with descriptions of each of the four disease entities, followed by an outline of the measures used in standard rheumatological care in Finland. Thereafter, we review the various aspects of healthcare utilization research in rheumatic diseases, and present the Finnish healthcare system. The emphasis is on health service-related direct costs, both for the index rheumatic disease and for multimorbidities. For JIA, we also explore the characteristics of the disease in adulthood.

2.1 Rheumatoid arthritis

2.1.1 Overview

In Finland, the approximated incidence of RA is at 45 per 100,000.[9] RA is a chronic inflammatory disease which generally manifests between ages 30 to 70, and has a female predisposition by a ratio of approximately 3 to 1.[9] Typically, it symmetrically affects small and medium-sized joints, particularly the hands and feet.

The genetic contributions of RA are complex. On the population level, the genetic factors account for approximately 60% of the variation in liability to disease.[10] Of environmental risk factors, smoking appears to be the most harmful.[11] Seropositivity currently refers to detection of (rheumatoid factor) RF or anti-citrullinated peptide antibodies (ACPA) from the blood, and seropositive RA is a fairly homogeneous disease. Current RA classification criteria from 2010 are based on collaborative work of American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR). It involves an individual score, based on assessment of four domains: number and site of involved joints, serologic abnormality, elevated acute-phase response, and symptom duration.[12] In line with current treatment paradigms, the focus of this classification system is on features of early disease.

2.1.2 Treatment and outcomes

Cogent evidence exists as to the decrease in morbidity and mortality of RA.[13-18] Despite the improved outlook, there still remain patients with poor or sub-optimal response to treatment.[19] Treatments aim to control the disease since no cure exists. The therapeutic target of RA follows the treat-to-target (T2T) strategy aiming at clinical remission or lowest achievable disease activity, with early, active treatment.[20,21]

The Finnish guidelines recommend pharmacological treatment initiation with a combination of csDMARDs and intra-articular glucocorticoid injections to treat inflamed joints (Figure 1).[22] Using combination therapy as the initial treatment has entailed excellent results, without a significant increase in adverse events.[23] If this first-line treatment fails, bDMARDs or targeted synthetic DMARDs (tsDMARDs) may be used, generally in combination with methotrexate (MTX).[24] Sometimes, after a sufficient period in remission on medication, tapering the dose or expanding the dose interval of a bDMARD may be considered individually.[24] In the combination treatment, tapering down one medication at a time, usually starting with glucocorticoids, is a common strategy. With discontinuation, disease activation and flares off medication are common and drug-free remission is reported in only 9 to 29%.[25] Therefore, the effective drug combination is often used as long as possible or necessary.

For all rheumatic diseases, the long-term safety of bDMARDs is an area actively investigated. For instance, recent evidence has found no substantial risk increase for cancer in bDMARD users, compared to bDMARD naïve patients treated with csDMARDs.[26] However, if an association is detected, it is uncertain whether it results from true causality or certain biases.[27] For instance, patients needing bDMARDs also have higher disease activity, which may affect the results.

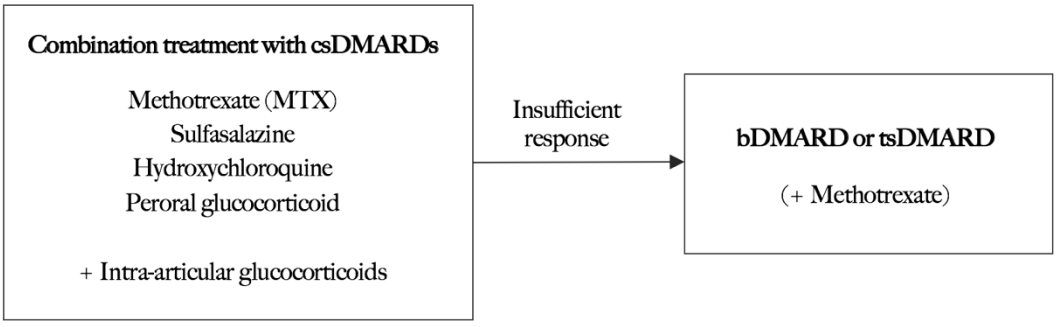


Figure 1. General treatment strategy for RA in Finland.

As part of an early targeted intervention, patient guidance is key, as is physician adherence to active treatment strategies.[28] In Finland, patient guidance in chronic rheumatic diseases relies on a multiprofessional team, which includes e.g. trained rheumatology nurses, physiotherapists, and occupational therapist.[29] In addition to pharmacological treatments, the current Finnish care guidelines emphasize the effect of physical training in maintaining physical function.[22]

Even in contemporary cohorts, patients with RA show worse work outcomes than general population comparators.[30,31] Many studies show considerable decrease in orthopaedic surgery for RA,[32,33] probably reflecting the effectivity of the modern DMARD treatment. One detailed analysis found that the rates of hand and foot surgery show a consistent decline from 1986 to 2011.[34]

2.1.3 Comorbidity

The main contributor to excess mortality in RA is increased cardiovascular disease (CVD) risk[35], highlighting the importance of investigating RA comorbidities. Approximately 6% of RA patients have suffered a cardiovascular event (myocardial infarction or stroke).[36] RA is associated also with various other comorbidities,[36,37] such as osteoporosis,[38] diabetes,[39], infections,[40] depression,[41] and hematological malignancies.[42-44] The goals in management of comorbidities in both RA and other inflammatory rheumatic diseases include prevention, early diagnosis and active treatment to try preventing long-term damage.

Systemic inflammation, in an interplay with traditional CV risk factors may drive the progression of CVD.[45-46] Reducing inflammation with MTX or bDMARDs may both improve endothelial function and reduce the risk of coronary heart disease (CHD) events.[47-48] Therefore, controlling disease activity to lower CVD risk is a key goal of the current EULAR recommendations for CVD risk management.[49]

The relations of RA and its comorbidities are complex. For instance, some comorbidities are features of RA itself, and some are at least partially linked to pharmacological treatments. Some examples fulfilling both of these criteria are the increased risk for severe infections[40] and gastrointestinal adverse effects.[37] Moreover, corticosteroid treatments increase the risk for both diabetes and osteoporosis. Smoking is a risk factor for both RA and lung cancer, which is known to be associated with RA.[50] Multiple domains of physical function and levels of fatigue are affected by increasing numbers of comorbidities.[51,52] Many RA patients are elderly, and aging in general increases the risk for multimorbidity.[53]

2.2 Juvenile idiopathic arthritis in adulthood

2.2.1 Overview

Rheumatic diseases in children are rare. The diagnosis "juvenile idiopathic arthritis" (JIA), comprises a diverse group of disease subtypes sharing chronic inflammation, usually chronic arthritis, as a common feature. JIA, sometimes referred to as juvenile rheumatoid arthritis (JRA) or juvenile chronic arthritis (JCA) is currently classified to categories (Table 1) according to the International League of Associations for Rheumatology (ILAR).[54] By definition, the symptoms present before age 16 and last for at least six weeks.[54] The diagnosis is made by detecting subtype-specific findings and by exclusion of other potential causes of the symptoms. In Finland, annually around 140 children fall ill from JIA, with a 70% female predilection.[55]

The clinical findings vary, particularly between subtypes.[56] A common extra-articular manifestation of JIA is uveitis[57], which seems to occur most frequently in the oligoarticular-onset subtype.[57,58] Studies suggest that uveitis prevalence and complications in children have decreased in the 21st century. [59,60] Another characteristic of JIA is active temporomandibular joint (TMJ) arthritis, seen in up to 75% of children with JIA and described in all subtypes. Given the potential damage to mandibular growth, long-term outcomes of TMJ arthritis are unfavourable.[61] However, also arthritis of the TMJ has benefited from the active treatment strategies and therapeutical advances.[62]

The etiology of JIA is unknown, but alike many other inflammatory rheumatic diseases, it is likely caused by an interplay of genetic and environmental factors. Overall, JIA subtypes are highly heterogeneous and recent biologic discoveries argue for an update in the classification system.[63] As an example, evidence implies that systemic JIA is biologically distinct from the other subtypes.[63,64]

2.2.2 Treatment and outcomes

Overall, treatment aims in JIA are inactive disease and full functional capacity. Treatments vary based on subtypes and symptoms, but early and aggressive treatment to target is key.[4,65] In Finland, MTX and intra-articular glucocorticoids are cornerstones of current pharmacological treatments in childhood. In addition, various other csDMARDs, such as leflunomide, sulfasalazine and oral glucocorticoids are used.[65] bDMARDs, a few of which are indicated in JIA, are in Finland generally used in patients who fail to respond to first-line treatments. Multidisciplinary therapy including physiotherapy, adequate eye examinations, and follow-up of a child's growth

and development are essential.[56] In adulthood, which is the focus of this thesis, the treatment patterns follow those of similar adult forms, such as the treatment of RA in JIA polyarthritis and oligoarthritis.

Despite occasionally being limited to childhood, for some, disease activity may persist into adulthood. The disease course is highly variable, and depends on disease subtype.[66] Table 1 summarizes the estimates of children and adults with active disease, using studies with long-term follow-up (over 5 years) and any subtype-specific information available. The estimates showed high variability, but the lower limits in children generally came from the more recent cohorts. The most favorable remission rates are apparent in persistent oligoarticular JIA[67,68] whereas extended oligoarticular, systemic, and polyarticular subtypes come with a worse natural disease course. [68-70]

Most studies have estimated that approximately a half continue in adulthood to have detectable inflammation.[69-71] Disease characteristics at 5 years of follow-up may better predict outcomes than would disease characteristics at disease onset.[66,69] In a 1980s Norwegian cohort of 176 patients, studied 30 years after disease, up to 59% of patients were in clinical remission off medication; those in remission on medication comprised 7% and active disease was present in 34%.[72] In another cohort, at 17 years of follow-up, only 40% were in remission.[66] One study published in 2002 found that in patients with long-standing JIA, severe disability defined as health assessment questionnaire (HAQ) over 1.5 was present in 42.9%.[58] However, even the more recent studies have involved patients with disease onset before the era of current treatment regimens. Moreover, studies of the impact of JIA on physical functioning and work ability in adulthood are few.

2.2.3 Comorbidities

Alike the aforementioned ocular involvement, many coexisting conditions are extra-articular manifestations of JIA. In regards of other comorbidities, the data published so far is limited and based on small patient populations, with even smaller numbers of patients with comorbidities.

An important distinction is the comorbidity in children and comorbidities occurring in adulthood, which is the focus of this thesis. Studies in children show an association with autoimmune diseases, such as diabetes, celiac disease, and hypothyroidism.[73-75] Most studies are underpowered to detect subtype-specific associations, but empirical evidence suggests that subtypes may differ in terms of the autoimmune comorbidities. Raab and colleagues investigated the self-reported comorbidity in young adults (mean age 19.7) recruited from a biologic register and found the highest comorbidity burden

Subtype	Arthritis	Additional criteria	Active disease in childhood (%)*	Active disease in adulthood (%)
Systemic JIA	1+ joints	Fever, rash, lymph node enlargement, hepatomegaly and/or splenomegaly, serositis	15-30 [76-79]	20-55[67,69,80]
Persistent Oligoarthritis	1-4 joints throughout the disease course	-	5-30[77-79,81**]	25-50[67,69,80]
Extended Oligoarthritis	1-4 joints during the first 6 months of the disease, 4+ joints after 6 months	-	5-60[77-79,81**]	35-80[67,69,80]
Polyarthritis (RF negative)	5+ joints during the first 6 months of the disease	RF negative	5-60[77-79,81]	50-70[67,69,80*]
Polyarthritis (RF positive)	5+ joints during the first 6 months of the disease	RF positive, 2 or more positive tests	5-65[77-79,81]	>90[69,80]
Psoriatic Arthritis	1+ joints	Arhritis and psoriasis, or arthritis and at least 2 of the following: 1) dactylitis, 2) nail pitting or onycholysis, 3) psoriasis in a first-degree relative	<5-55[77-79]	55[69]
Enthesitis-related arthritis	1+ joints	Arthritis and enthesitis, or arthritis or enthesitis with 2 or more additional criteria, e.g. HLA-B27 antigen, acute anterior uveitis, or sacroiliitis with inflammatory bowel disease	5-60[77-79,81]	45[69]
Undifferentiated arthritis	1+ joints	Does not fulfill criteria of any other category or fulfills 2 or more of the other categories	0-50[77-79]	0[69]

* Long-term follow-up

** Extended vs persistent subtype not distinguished in all studies

Table 1. Current JIA subtypes according to ILAR Taskforce on Classification of Childhood Arthritis, along with estimates from the literature for the proportion of children and adults with active disease after long-term follow-up (over 5 years). See the original article on JIA subtypes for diagnostic exclusion criteria and a more extensive description of the additional criteria.[54]

for systemic-onset JIA. In all subtypes, uveitis was the most common comorbidity (17.7%), followed by allergic rhinitis (14.5%), CVD (9.9%, no CHD detected), migraine (8.7%), and atopic dermatitis (8.7%).[82]

Comorbidities become more prevalent when patients with JIA grow adult and become elderly. The long-term risk of CVD in JIA is uncertain,[83,84] but based on shared pathophysiology with certain adult forms of inflammatory arthritis, some subtypes of JIA may share their comorbidity spectrum.

Like for other rheumatic diseases, the safety of bDMARDs is closely monitored. In patients with JIA who have used bDMARD, the risk of malignancies, particularly lymphoproliferative malignancies is elevated compared to the general population, but the absolute risk is still low [85] and channeling bias may exist.

2.3 Psoriatic arthritis

2.3.1 Overview

In patients with psoriasis, PsA occurs in approximately 6-41%, but the estimates vary considerably, also according to psoriasis severity.[86] The incidence in Finland is estimated at 23/100 000/year.[87] Age of onset range is wide, but in men the highest incidence is around ages 30 to 39.[88] The clinical appearance is heterogeneous and may affect distal joints, particularly the joints of fingers and toes but also axial or large joint involvement occur.[89] Peripheral arthritis may be symmetrical or asymmetrical and overall, this polymorphic disease may present with symptoms resembling both RA and AS. Nail symptoms, dactylitis, and enthesopathies are common, recurrently occurring features of PsA.[90] The diagnosis is clinical.

Although the etiopathogenesis is still somewhat unknown, insights gained from biomedical studies suggest involvement of T-cells in particular. Particularly the early-onset forms of PsA and psoriasis show a higher hereditary component and more familial aggregation,[91,92] but in general, the disease is thought to result from an interplay of environmental factors and immune factors in patients with genetic susceptibility.[90,93] Much of the genetic basis of psoriatic disease and PsA resides within the human leukocyte antigen (HLA) region,[91,94] which also might contribute some of the epidemiological findings suggesting gender predilection.[88,91]

2.3.2 Treatment and outcomes

Appropriate care involves treating all the disease manifestations: the skin and the nails, if involved, and the joint symptoms, including back pain, enthesitis, and dacylitis. Overall, the treatment is tailored to the needs of individual patients and their combination of symptoms. The mainstay treatments for musculoskeletal symptoms are non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular glucocorticoid injections. If chronic inflammation is detected, csDMARDs are introduced early. Of csDMARDs, MTX is the commonly used in Finland; it also alleviates skin symptoms. Some alternatives include leflunomide and apremilast. Sufasalazine is used for PsA with axial involvement, although its mechanism of effect for alleviating these symptoms is poorly documented. Sulfasalazine does not alleviate the skin symptoms of psoriasis. Many bDMARDs are approved for PsA, and also tsDMARDs are currently reimbursed for PsA. Physical therapy, occupational therapy, and exercise recommendations are similar to those of other inflammatory rheumatic diseases.

The disease course is heterogeneous: most patients manifest a relatively benign disease with little progression, but some have progressive disease. Some studies suggest that the health-related quality of life and overall disease burden may be quite similar in patients with RA and patients with PsA, although those with PsA may show a slight tendency towards worse outcomes.[95,96]

2.3.3 Comorbidity

Extra-articular manifestations include ocular involvement in form of uveitis, particularly in the axial form of PsA. PsA comes with an increased comorbidity burden both years prior and after the diagnosis.[97] Psoriasis alone as well as PsA in patients with psoriasis, particularly moderate-to-severe psoriasis, is associated with a comorbidity burden and higher healthcare utilization.[98-100]

Patients with PsA are at risk for risk of diabetes, hypertension, hyperlipidemia, hyperuricemia, and other metabolic risk factors.[39,98,101-103] Studies from specialty clinics have detected increased mortality dependent mainly on CVDs, but this finding is unsupported by population-based studies.[104,105] The association with CVDs may result from the metabolic risk factors, such as hypertension, high triglycerides, and high body mass index (BMI), which are more prevalent in individuals with PsA than in the general population,[106] and more prevalent than in patients with psoriasis alone or RA.[107] Addictions such as alcohol abuse in patients with psoriasis are increasingly

appreciated in the literature.[108-110] For instance, compared with the general population, patients with psoriasis have approximately a 60% greater risk of dying due to alcohol-related causes.[109] However, similar studies on patients with PsA are almost non-existent.

2.4 Axial spondyloarthritis

2.4.1 Overview

Spondyloarthropathies (SpA) is an umbrella term covering inflammatory rheumatic diseases affecting the spine, ones such as reactive arthritis, and also arthritis or spondylitis associated with inflammatory bowel diseases. AxSpA is a form of spondyloarthritis in which the predominant symptom is back pain, and where radiographic sacroiliitis may or may not be present. If definite radiographic sacroiliitis is present in imaging, the disease can be classified as ankylosing spondylitis (AS). AxSpA comprises both the classic form of AS along with non-radiographic axial spondyloarthritis; these are nowadays increasingly considered as consecutive stages of one single disease.[111,112]

SpA presents with a range of clinical features,[111] but many studies point toward a common pathophysiologic foundation for this clinically interrelated disease entity.[113] Patients may also manifest arthritis in the peripheral joints, and may present with enthesitis, which involves inflammation at tendon-, ligament- or joint-capsule insertions.[114] The term "spondyloarthropathy" generally refers to an inflammatory disorder of the back, whereas spondyloarthritis implies that inflammation is detectable.

The global prevalence of SpA is about 1%,[111] with the estimated incidence in Finland being 7/100,000 for AS, and 53/100,000 for SpA,[87] but with much variation in the estimates.[111,115] The typical onset is in young adulthood. Gender predilection seems to vary between different disease manifestations.[112,115-117] Genes within and outside the major histocompatibility complex (MHC) region, particularly HLA-B27 confer susceptibility to disease, but environmental triggers are expected to play a key role in causing the disease.[118,119]

2.4.2 Treatment and outcomes

The ASAS-EULAR management recommendations for AxSpA list five overarching principles for disease management: 1) AxSpA is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary management coordinated by the rheumatologist, 2) the primary goal of treating the patient with axSpA is to maximise long-term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalisation of function and social participation, and 3) the optimal management requires a combination of non-pharmacological and pharmacological treatment modalities, and that 4) the treatment must be based on a shared decision between the patient and the rheumatologist, and 5) axSpA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.[120]

NSAIDs are a mainstay treatment in AxSpA, being effective both in alleviating pain and perhaps even in slowing down radiological progression.[121] In Finland, if NSAIDs are insufficient, treatment with csDMARDs such as sulfasalazine is attempted prior to bDMARDs. This is also required for reimbursability of bDMARDs, which are used when patients present with moderate to severe pain in combination with high disease activity.[120,121] Exercise is important in maintaining and improving physical functioning, with most of the existing evidence concerning AS.[122]

Large advances have occurred in the field of AxSpA during the 2010s in classification, basic science, and therapeutics.[123] Disease progression is usually slow, with mild symptoms at onset, but progression rates show high individual variability. A better understanding of the full spectrum of disease has facilitated disease identification at earlier stages. Reports on work outcomes show large variations between countries, but the risk for work disability is high both at baseline and later in the disease course.[124,125] Even within countries, considerable variation exists in work outcomes.[31]

2.4.3 Comorbidity

Features of the disease include extra-articular manifestations such as uveitis, psoriasis, and inflammatory bowel disease, with their prevalences at 25.8%, 9.3%, and 6.8%.[126] An important comorbidity to consider is the CVDs. In a meta-analysis comparing individuals with AS to rheumatic disease-free controls, those with AS had an odds ratio of 1.6 for myocardial infarction and an odds ratio of 1.5 for stroke.[127] A more recent study by Eriksson comparing the CVD risk of AS patients to that of RA patients and

the general population identified a somewhat similar risk increase of 30%–50% compared to that of the general population. Compared to patients with RA, the risk increase in AS was similar for stroke, but only half as high for acute coronary syndrome and thrombotic events.[128]

In a study by Ara et al on AS, 50% of patients had at least one comorbidity, the most common being CVD with angina being present in 7%, hypercholesterolaemia in 10%, and hypertension in 17%.[129] A recent meta-analysis reports the pooled estimate of moderate to severe depression to be 15%, and many studies report higher disease activity in patients with depression.[41] Overall, comorbidity in SpA is also associated with worse work outcomes.[124]

2.5 Pain-sensitivity syndromes

Fibromyalgia is a disease considered part of a spectrum of disorders with similar biopsychosocial underpinnings and pain mechanisms, namely centralized pain due to a central disturbance in pain processing, as opposed to nociceptive pain (inflammation or mechanical damage) or neuropathic pain (damage, injury or dysfunction in peripheral nerves). This spectrum, called central sensitivity syndromes, a term proposed by Yunus[130] and adopted by many others,[131-133] comprises diseases such as chronic pelvic pain, chronic fatigue syndrome, chronic low back pain, irritable bowel syndrome, and temporomandibular joint disorders.[131,134,135]

More prevalent in women and in those of low socioeconomic status, fibromyalgia has an estimated worldwide prevalence of 2.7%.[136] Its diagnosis is arrived at by detecting characteristic clinical findings and symptoms,[137] supported by assessment of the tender points. The clinical manifestations are multifaceted, with the hallmark symptom being centralized pain with hyperalgesia (abnormally increased sensitivity to pain) and allodynia (pain from a stimulus which would not usually provoke pain). Other common symptoms include sleep disturbances such nonrestorative sleep, weakness, fatigue, and mood disorders, symptoms often shared with the other central sensitivity syndromes.[137-140] Genetic, environmental, and neuropsychiatric factors are considered to predispose to the disease, although the ethiopathogenesis is highly debatable.[140-144] In a recent Finnish study on the long-term outlook of fibromyalgia, most patients' symptoms persisted over the 26-year follow-up, but fluctuation and even long symptomless periods were detected in many.[145]

The most recent EULAR recommendations on management of fibromyalgia strongly support the role of exercise and patient education and these two are also recommended as key initial therapies. If further therapies are needed, the

recommendation highlights the need for tailoring the therapy according to individual needs. For most other treatment strategies, both pharmacological and non-pharmacological ones, evidence is weak, and the effect is considered modest at most. Pharmacotherapy, for instance with low-dose amitriptyline, is recommended mainly for moderate to severe fibromyalgia or sleep disturbances.[146]

In most rheumatic diseases, pain is common symptom and therefore a core domain measured and targeted actively.[147] The pain associated with rheumatic diseases is multifactorial: it may result from joint-related causes such as active inflammation or chronic joint destruction, but pain-regulation mechanisms may also be altered.[148,149] Modeling the different pathways of pain in rheumatic diseases has underscored the link between cognitive, behavioral, and emotional processes such as pain catastrophizing and physical disability, depression, and decreased quality of life.[149,150] In addition, fatigue is a major concern,[151-153] and estimates of severe fatigue range from 41% to 57% of patients with RA, AS, PsA, scleroderma, or systemic lupus erythematosus.[154]

Several studies have detected a higher prevalence of fibromyalgia in patients with RA compared to the prevalence in the general population. Compared to those with isolated RA, RA patients with fibromyalgia show worse patient-reported outcomes and higher levels of disease activity, particularly due to increased sensitivity to pain.[155-158] These challenges are also recognized in the EULAR recommendations for management of fibromyalgia, where the authors announce the need for studies on how fibromyalgia should be managed when it occurs as a comorbidity to inflammatory arthritis.[146]

2.6 Measuring disease activity

Of the multiple existing measures for RA disese activity, DAS28 is extensively validated and is considered to be the gold standard by which to measure disease activity and its changes as a response to treatment.[159] DAS28 with three items (DAS28-3) involves assessment of the tender and swollen joints based on the 28-joint count, as well as a measurement of inflammatory markers, either erythrocyte sedimentation rate (ESR, mm/h) or C-reactive protein (CRP, mg/l). If DAS28 with four items (DAS28-4) is used, it involves the also patient's assessment of general health. More technical descriptions will be presented later. DAS28 thresholds for disease activity are often >5.1 for high disease activity, ≥3.2 for moderate disease activity, <3.2 for low disease activity, and <2.6 for low/minimal disease activity or remission.[159]

2.6.1 Challenges in measuring disease activity

Multiple challenges in measuring DAS28 exist.[160,161] ESR and CRP are not disease-specific, and may rise due to infection or to other chronic diseases, as well. Fibromyalgia and other chronic pain may impact the tender-joint count, resulting in disproportionately high counts compared to the swollen joint count. Therefore, although DAS28-3 and DAS28-4 agree quite well at a group level, in individual patients the difference may be substantial due to the patient's general health assesment.[162,163] The score is also subject to variation between observers. More extensive joint counts exist, but they are used more often in clinical trials than in regular care,[160,164] whereas the reduced 28-joint counts has shown comparable potential in RA in terms of ability to detect change over time.[165-167] The 28-joint count, however, excludes the metatarsophalangeal (MTP) joints, the joints in the foot between the metatarsal bones and the proximal bones of the toes, which are commonly affected in RA, as well as the ankles.

2.6.2 Measuring disease activity in other inflammatory rheumatic diseases

As earlier described, DAS28 is suitable for measuring disease activity in RA. Although used in clinical trials and in clinical care, the 28-joint count and DAS28 are not optimal for other inflammatory rheumatic diseases.[164,168] These ratings may underestimate the disease activity due to the complexity of symptoms seen in other inflammatory rheumatic diseases, such the asymmetry of symptoms often seen in PsA, or spinal manifestations in AxSpA. DAS28 excludes the distal interphalangeal joints (DIP) of the fingers, which are commonly affected by PsA, but not by RA. Importantly, it doesn't capture the extra-articular manifestations occurring in many rheumatic diseases.

Due to these limitations, specific disease activity indices have been developed for both PsA and AS, some of which are used and applied mostly in clinical trials. Many of these scores involve more extensive joint counts and/or information about extra-articular manifestations of disease. Examples of these disease-specific scores are Disease Activity in Psoriatic Arthritis (DAPSA), the Composite Psoriatic Disease Activity Index (CPDAI), and the Ankylosing Spondylitis Disease Activity Score (ASDAS).[169-174] The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a fully patient-reported measure for disease activity.[175] BASDAI, similarly to other patient-reported measures, may lack specificity to the disease for which it was developed: for instance, patients with fibromyalgia may report higher BASDAI values than do those with SpA.[176]

The most commonly used JIA-specific disease activity score, the juvenile arthritis disease activity score (JADAS), was developed in children and comprises four measures: physician global assessment of disease activity, parent/patient global assessment of wellbeing, active joint count, and ESR.[177] Three versions exist, with 71-joint, 27-joint, and 10-joint counts. In patients with JIA whose disease has continued into adulthood, treatment patterns follow those of similar adult forms, such as the treatment of RA in JIA polyarthritis and oligoarthritis. Therefore, JIA patients followed up in adult rheumatology clinics are often evaluated with DAS28. Among children, adolescents, and adults, DAS28 and JADAS have shown moderate to strong correlation.[168,177,178] Defining the disease activity criteria has been challenging even in children,[179-181] with very little data on how these apply in adults.

Although DAS28 includes a larger joint count than does JADAS-10, it still may underestimate disease activity perhaps because JADAS incorporates joints outside those included in DAS28.[168] The JADAS-10 is based on the count of any joint involved, up to a maximum of 10 joints.[177] Another noteworthy limitation is that neither JADAS nor DAS28 involves assessment of uveitis, an important extra-articular manifestation on JIA. At the time of JADAS development, no standardized grading of uveitis activity was available, although some definitions of clinical inactive disease involve uveitis defined by the Standardization of Uveitis Nomenclature (SUN)[181,182] However, the SUN Working Group has embarked on a second phase to forge a better consensus for terms used for uveitis.[183]

2.7 Patient-reported outcome measures in rheumatic diseases

Measures involving patient-perceived symptoms have reflected changes in disease outcomes such as disease status[184-186] and disability.[187-189] They have therefore become a prominent part of both standard rheumatological care and research; minimising these symptoms experienced by the patient is one of the main treatment goals. Although RA has received the most attention in outcomes research, similar measurements and core domains for patient-reported outcomes are applied in the other rheumatic diseases.[147,186]

Multiple patient-reported outcome measures have been developed and validated for assessing disease activity in RA.[190] The patient's assessment of global health or wellbeing, for instance on a scale from 0 to 10, is integrated into many disease activity indices, including the DAS28 with four items.[159,191] The visual analogue scale (VAS) for

pain and fatigue, and the HAQ disability index for disability are among the most commonly applied tools, and were studied in this thesis.

Several challenges in measuring patient-reported outcomes must be considered. Symptoms perceived by patients are affected by multiple factors such as age, sex, social, and socioeconomic factors, and by cognitive impairment.[192-194] Importantly, the results of patient self-assessment are not specific to any level of inflammation, nor do they necessarily correlate with the physician-detected disease activity.[163,184,195] In addition, considerable variation may exist between the sexes and among different age groups.[196] Diversity of languages and cultures is a challenge in translating the instruments,[197] and this may impact comparability of mean scores between countries.

2.7.1 Measuring health-related quality of life

RA and other inflammatory rheumatic diseases make a substantial impact on health-related quality of life (HRQoL).[198,199] Increasingly measured in rheumatological research, HRQoL can be defined as the impact of health on an individual's ability to function and on perceived well-being in the physical, mental and social domains of life.[200] Due to high overlap between the commonly utilized patient-reported outcomes, such as pain, function, and patient global assessment, some view all of these as HRQoL measures.[147]

Hundreds of instruments exist to measure HRQoL, but in rheumatic diseases, generic instruments are most often used. These include the popular used 36-item Short-Form Health Survey (SF-36), the EuroQol instrument (EQ-5D) utility index, and the Finnish 15-dimensional quality of life questionnaire (15D).[201-203] These instruments cover a variety of disease-related factors and aspects of mental and social health, such as mobility, vitality, and depressiveness. None of them has been proven to perform uniformly best, and the choice of instrument depends on characteristics of the population and the setting in which it is used (e.g. routine care or clinical trial).[200] In addition, to measure aspects relevant to rheumatic diseases, specific tools have been developed, including RAQoL for RA and the PsAQoL for PsA.[204,205]

2.7.2 Measuring functional disability

Although many definitions for disability exist, one highly cited definition is the following by Leonardi and colleagues: *"Disability is a difficulty in functioning at the body, person, or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors."* [206] The definition encompasses the functional, psychological, and social aspects of disability.

This section aims to provide an overview of instruments for measuring the physical and functional aspects of disability in rheumatic diseases.

Questionnaires involving assessment of functional status provide a valuable prognostic measure for multiple long-term outcomes of RA, including work disability, joint replacement surgery, and mortality.[187-189,207] The Health Assessment Questionnaire (HAQ), published in 1980, was developed to assess the functional status in adults with arthritis. It is validated by numerous studies, and translated or culturally adapted into more than 60 different languages and dialects, often with only minor changes.[208,209]

The disability component of HAQ, the HAQ disability index or "legacy HAQ," is the tool most widely used for quantifying functional disability in rheumatic diseases. Multiple modifications to assess disability have been developed,[209] such as the modified HAQ (MHAQ),[210] the multidimensional HAQ (MDHAQ),[211] and HAQ-II.[212] Most of the modifications are shorter versions of the HAQ. Usually the recall period is one week. The modified instruments often serve as a substitute for the original HAQ disability index in both clinical care and in research and they have shown reliability and validity similar to that of the original HAQ disability index,[209] although in particular the MHAQ has received criticism as lacking sensitivity to change and as missing certain aspects of functional impairment.[213,214]

To calculate the HAQ disability index, the patient evaluates each item in the questionnaire (Table 2) and selects one of four alternatives that best matches the patient's own situation during the past week, in points: can perform the act without any difficulty (1 point), with some difficulty (2 points), with much difficulty (3 points), or the patient is unable to do it (4 points). The highest points for each section represent the points for the section. The points are then added up, and the resulting raw HAQ is then divided by 8 to calculate the final HAQ disability index, which ranges from 0 to 3. The HAQ measurements in this thesis were made by measuring the level of disability without any aids or devices, which would affect the interpretation of the score.

Cutoffs for the HAQ disability index vary, although the usual cutoffs are the following: 0 to 1 for no to mild disability, 1 to 2 for moderate to severe disability, and 2 to 3 for severe to very severe disability. However, values over 2 are rare, particularly as the current treatment paradigms for rheumatic diseases aim for full functional capacity.

These disability indices are commonly used for evaluating disability in the various rheumatic diseases but disease-specific instruments also exist. The most popular instrument for AxSpA is the Bath Ankylosing Spondylitis Functional Index (BASFI),

a quickly completed patient self-assessment of eight items relevant to everyday tasks (bending, reaching, changing position, standing, turning, and stair-climbing) and two items for the ability to cope with everyday life.[215] Relevant pitfalls described for BASFI include clustering toward the low-disability end of the distribution and the fact that it may lack sensitivity to detect subtle changes in function in patients without severe disability.[171,174] In patients with PsA with or without axial involvement, BASFI shows a high correlation with other instruments for measuring functional disability, such as the HAQ, therefore offering only a limited advantage over the HAQ disability index.[216]

Functional disability is not unique to patients with rheumatic diseases: in a survey of a random general population sample of 1,530 individuals living in central Finland, the average HAQ disability index was 0.25, with 32% of the whole sample showing at least some disability.[196] The normative values for HAQ vary by sex and age,[196] and differing sociodemographical factors can produce response bias in the individual HAQ items, although the impact on composite HAQ indices is estimated to be minor.[217]

Item	
1	Dress yourself, including shoelaces and buttons Shampoo your hair
2	Stand up from a straight chair Get in and out of bed
3	Cut your own meat Lift a full cup or glass to your mouth Open a new milk or juice carton
4	Walk outdoors on flat ground Climb up five steps
5	Wash and dry your whole body Get on and off the toilet
6	Reach and bring down a 2-kg object from above your head Bend down to pick up clothing from the floor
7	Open car doors Open previously opened jars Turn faucets on and off
8	Run errands and shop Get in and out of a car Do chores such as vacuuming or yard work

Table 2. The health assessment questionnaire (HAQ) items for calculating the HAQ disability index.

2.7.3 Measuring pain and fatigue

Pain and fatigue are core symptoms experienced by patients with rheumatic diseases. Aspects of pain are also captured by the disability and quality of life questionnaires.[151] In rheumatological care, pain and fatigue are usually measured in a similar way: the patient reports the symptom experienced during the past week, often measured on a 10-cm visual analogue scale (VAS), which is then translated to a range from 0 to 100, in which 0 indicates no pain, and 100 the most severe pain imaginable. A clinically meaningful change in pain VAS is considered to be 10 mm.[218]

Multiple ways to measure fatigue in rheumatic diseases exist, but the single-item measures on a VAS or on a numeric rating scale are the most commonly used. Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) provides a global score based on 13 items regarding physical fatigue, functional fatigue, emotional fatigue, and social consequences of fatigue.[219,220]

2.8 GoTreatIt monitoring

2.8.1 Overview

In their daily work, rheumatologists combine information from patient examination, imaging and lab modalities, and most importantly, information about the patient's medical history, current symptoms, and self-reported function in activities of daily living. Patient monitoring is considered an important part of rheumatology, and this practice has arisen particularly from the need to measure outcomes and to be able to detect patterns which could potentially lead to disability and other poor disease consequences.[161]

Monitoring also aids both in clinical decision-making and in monitoring the potential adverse effects of medications. Multiple trials and reviews have highlighted the importance of quantitatitative monitoring for improving disease outcomes in RA.[161,221,222] The TICORA study (tight control for rheumatoid arthritis)[221] and the Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo)[222] are two well-known examples of the effect of tight control on outcomes in rheumatoid arthritis. This principle is also followed by the EULAR recommendations for management of rheumatoid arthritis.[223]

However, the quantitative monitoring of musculoskeletal conditions is more challenging than monitoring variables such as cholesterol levels in cardiovascular

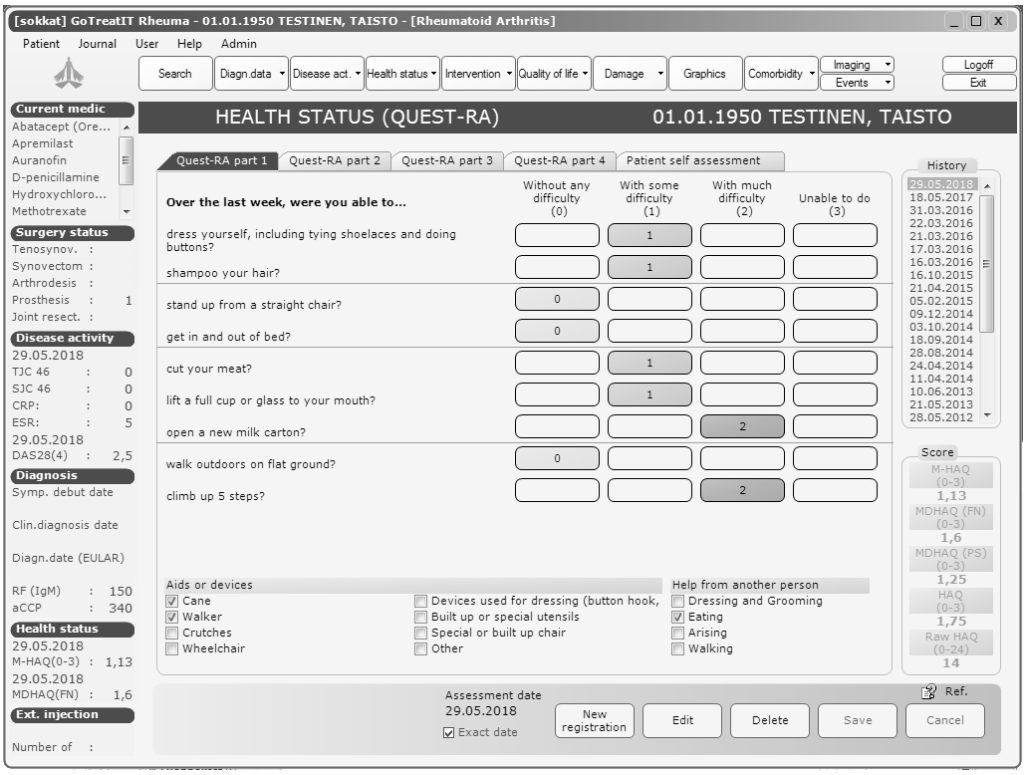
diseases.[224] One critical obstacle to monitoring, detecting patterns over a long periods of time, can be overcome by user-friendly information-technology solutions that collect information from different sources. One of these, the software GoTreatIt, was developed in in Kristiansand, Norway, by DiaGraphIT and it is widely used in Nordic countries as part of standard rheumatology practice.[29,96,225] With GoTreatIt, the main goal for monitoring is to improve patient care, but the collected data can also be utilized in research.[226]

GoTreatIt data are collected as part of standard care and the reliability of the data resides on the physicians, nurses, and medical secretaries who work in the clinic. The same data are utilized for a nation-wide register for biological treatment in rheumatic diseases (ROB-FIN), which provides observational evidence on the safety, effectiveness, and costs of bDMARDs and other medications. In Finland, monitoring data are currently being assembled and assessed for a national quality register for rheumatic diseases.

2.8.2 What is measured

Monitoring with GoTreatIt has been applied as standard care in the JCH since 2007. The clinic has developed a model to provide a one-stop service to avoiding unnecessary visits, collect structured patient data, and to enhance the patient experience.[29] When arriving for a scheduled outpatient visit in the rheumatology unit in the JCH, patients fill in questionnaires on computers specifically serving this purpose in the waiting room – currently patients can also complete the questions remotely using their cell phone or personal computers. The questionnaires include pain, fatigue, global health, assessment of disease activity on a VAS, the HAQ disability index, and painful joints. This information is then transferred electronically to the rheumatologist who can inspect it prior to the appointment (Figures 2 and 3, Table 3).

During the appointment, the rheumatologist documents any findings (including swollen and tender joints) and records any medication initiations or changes. The laboratory values, ESR (mm/h) and CRP (mg/l), are imported from the laboratory system, and can be graphically displayed alongside medications and patient-reported outcomes. In addition, the software calculates DAS28-ESR and DAS28-CRP scores for current disease activity by the formulas in Table 4.[227]



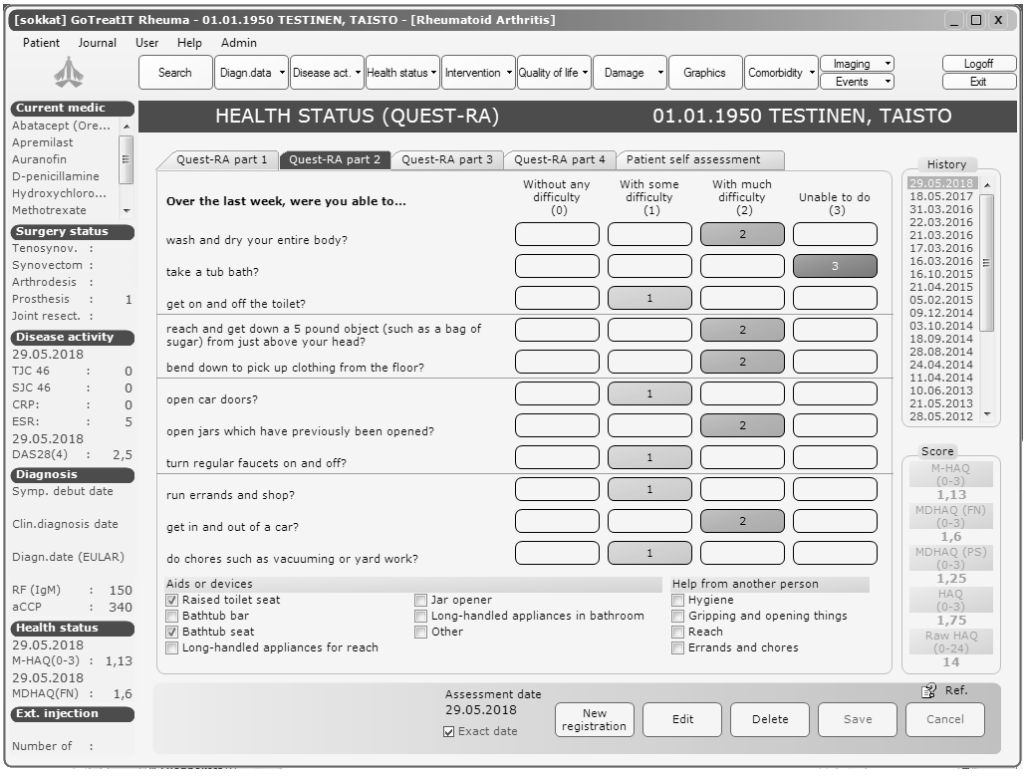


Figure 2. The graphical display of GoTreatIt monitoring showing questions of the Health Assessment Questionnaire.

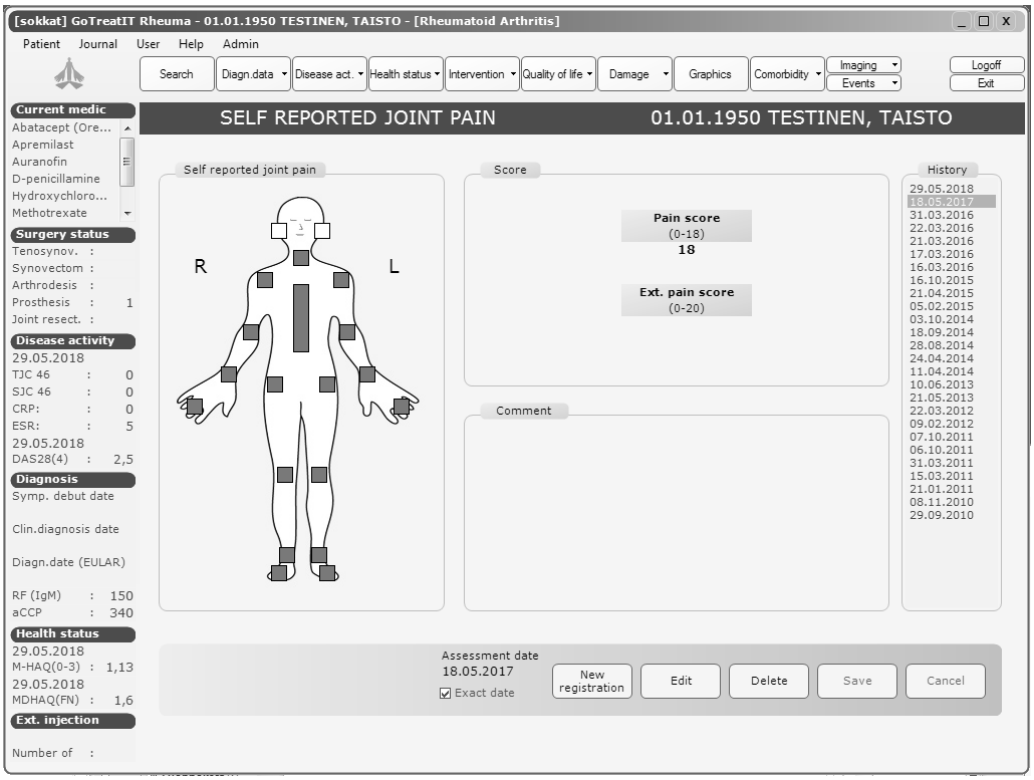


Figure 3. The graphical display of GoTreatIt monitoring.

HEALTH STATUS

Date	21.03.2016	22.03.2016	31.03.2016	18.05.2017	29.05.2018
Pain	61	78	88	52	89
Fatigue	60	76	90	97	53
Patient global	60	77	73	78	99
Morning stiffness	0.25	0.08	0.17	0.75	1.50
Rheumatic activity	30	32	0	49	71
Joint pain	79	26	25		64
Back pain			11		75
Back pain at night			28		72
Change of condition	Worse	The same			

Table 3. An example of the patient-reported outcomes displayed.

DAS28-3 (ESR)	0.56 x sqrt(TJC28) + 0.28 x sqrt(SJC28) + 0.7 x ln(ESR) x 1.08 +0.16
DAS28-4 (ESR)	0.56 x sqrt(TJC28) + 0.28 x sqrt(SJC28) + 0.7 x ln(ESR) + 0.014 x GH
DAS28-3 (CRP)	[0.56 x sqrt(TJC28) + 0.28 x sqrt(SJC28) + 0.36 x ln(CRP + 1)] x 1.10 + 1.15
DAS28-4 (CRP)	0.56 x sqrt(TJC28) + 0.28 x sqrt(SJC28) + 0.36 x ln(CRP + 1) + 0.014 x GH + 0.96

Table 4. Formulas for calculating the disease activity index. TJC28 = tender joint count based on the 28-joint count. SJC28 = swollen joint count based on the 28-joint count. GH = patient's assessment of general health on a scale from 0 to 10.

2.9 Health economics – general concepts

In addition to measuring the clinical outcomes of disease, another important outcome aspect to measure is the overall cost of the disease and the cost and consequences of interventions. In regard to the troubling increase in health care expeditures worldwide and the emerging, often costly, personalized therapies such as individualized cancer therapies, efficient resource allocation in health systems is crucial. This section aims to give an overview of economic evaluation in healthcare in general.

2.9.1 Overview of study settings

Cost-of-illness (COI) assessment of the economic burden of illness on society was the first economic evaluation technique in the health field.[228] Table 5 summarizes common economic evaluations, many of which focus on comparison of the relative value of alternative courses of action, in terms of both their costs and consequences.[228-231] In these comparative analyses, the comparator has a monetary value, whereas the outcome valuation varies by study type. Both the cost-effectiveness (outcome in natural units) and cost-utility analyses (outcome in utilities, e.g. quality-adjusted life years, QALYs) are common in comparison studies. However, cost-utility analyses are often referred to as cost-effectiveness studies, and many studies perform multiple types of analyses. One benefit of a cost-utility analysis is that it allows broad comparisons of various interventions accross the health sector. Incremental cost-effectiveness ratio (ICER) refers to the ratio calculated by dividing the incremental cost of the new intervention by the resultant incremental change in effectiveness. This ratio reveals the additional cost that an intervention imposes as compared to the additional benefit it delivers.[230,231]

Analysis	Objective	Outcome valuation	Drawbacks	Example
Cost of illness	Assessment of the economic impact of an illness or condition	None	Descriptive, impact on decision-making unclear	Analysing the total costs, and cost changes over time in RA[232]
Cost-minimization	Which is the least costly among alternative interventions assumed to produce equivalent outcomes?	Assuming equivalent outcome	Only outcomes measured in the same units can be compared	The overall costs of nonsurgical management of acute Achilles tendon rupture were significantly lower than were costs of surgical management[233]
Cost-effectiveness	Comparison of costs with outcomes in non-monetary units	Clinically relevant natural units	Inability to make interdisease comparisons	Mean cost to achieve remission with adalimumab €66,057[234]
Cost-utility	Comparison of costs with outcomes in non-monetary units	Utilities, e.g. QALYs	Challenges regarding the utility measures	In biologic-naïve AS patients, secukinumab dominated all comparators, with the highest QALYs (16.46) at the lowest cost (CAD 533,010)[235]
Cost benefit	A monetary value placed on outcomes	Monetary	Challenging to assign monetary value to all relevant outcomes	Implementing an exercise program to reduce falling in RA patients would result in £234,583 of savings with a net benefit of £118,104[236]

Table 5. Common types of economic evaluations in health economics research. QALY = quality-adjusted life years, CAD = Canadian Dollars.

The analyses in this thesis fall under the category of cost-of-illness studies. The study setting itself has been highly questioned by many health economists as to its usefulness in decision-making. However, it can inform decision-makers if considered from the proper perspective, one which asks innovative research questions, is capable of measuring the true cost to society, draws its data from the actual clinical management of illness, and assesses factors explaining cost variability.[228]

2.9.2 Analysis attributes

Direct and indirect costs are the main way of quantifying costs: direct costs refer to costs associated with medical care expenditures (diagnosis, treatment, medications), and indirect costs generally refer to the productivity losses related to the illness, such as sick leaves and disability pensions, commonly measured by the human capital approach (HCA) or the friction cost method (FCM). HCA determines the productivity loss by estimating the individual's expected future earnings, whereas the FCM assumes that the work input may be covered by others, thereby providing lower productivity costs than does the HCA.[237-239] Intangible costs represent a variety of expenses which are hard to measure, such as pain and deterioration in quality of life. Another cost component that is challenging to measure is informal care, which is a component of direct costs comprising care provided by caregivers outside of healthcare, such as family and friends.

Two key attributes need to be selected in comparison studies: 1) the outcome or endpoint, and 2) the comparator, which often is either the current standard care approach or no intervention.[230,240] The costs and disease outcomes are commonly collected within randomized controlled trials or from administrative databases. Analyses can be undertaken from a societal or a healthcare sector perspective. The societal perspective incorporates all costs and outcomes regardless of who incurs the costs and who obtains the effects, whereas the healthcare sector perspective seeks to maximise population health within a fixed healthcare budget, where the costs are borne from formal medical care.[230]

As costs and associated endpoints often do not accrue steadily over time, several attributes related to time need consideration. Importantly, the time horizon needs to be selected, although it is not always possible to obtain data for all optimal time frames. Studies comparing costs or cost-effectiveness across different years should adjust costs for inflation. As costs and outcomes occurring in the future often have less value than costs and outcomes realized today, discount rates should be applied if the study spans multiple years. Theoretical evidence points to adopting different discount rates based

on the analytical perspective (societal, healthcare sector) chosen.[241] Moreover, the commonly applied discount rate of 3% per annum[230] may result in systematic biases against interventions with high upfront costs but long-term benefits (e.g. vaccinations) in favour of interventions where the costs and health effects hold a more similar time profile (e.g. maintenance of chronic conditions).[241] Sensitivity analyses building different scenarios are to be recommended, particularly ones acknowledging aspects of uncertainty.[230,240,242] For instance, analyses using intermediate outcomes or applying a range of discount rates deserve encouragement. [230,240,242]

2.9.3 Factors affecting healthcare expenditures

In addition to the disease- and intervention-specific factors assessed in economic evaluations, a broader view of the health system should be considered when conducting these studies or when assessing published evidence. Table 6 lists important factors affecting healthcare expenditures,[243-250] making a somewhat artificial division into 1) factors arising from healthcare systems and social services, both of which are strongly affected by political decision-making, and to 2) other factors such as disease burden and sociodemographic factors. Most of these are, however, highly heterogeneous and in a complex fashion interlinked, and vary between high- and low-income countries.[245,251] Although age is a sociodemographic factor, because population ageing is an important driver of costs on every level, it is therefore highlighted separately.[243,252] Considering this thesis, the heterogeneity of these factors affecting healthcare expenditures also underlie the between-country discrepancies often seen in cost-of-illness studies, which also hampers detailed comparisons to prior studies.

Healthcare and social services	Other
Healthcare funding sources	Disease burden
Supply and demand of health services	Sociodemographic factors
Education of healthcare professionals	Population ageing
National income	Culture and religion
Social security	Environment
Disability benefits	Technology adaptation

Table 6. Factors affecting healthcare expenditures, many interlinked in a complex fashion.

2.10 Diagnosis Related Group (DRG) and DRG-like patient classification systems

With over a thousand existing diagnosis codes in, for instance, the ICD-10 (International Classification of Diseases, 10th Revision), further classification for both operational and research purposes is useful. Diagosis-related group (DRG), a patient classification system, was initially developed in the 1970s at the Yale university, to identify "products" provided by the hospital to the patient.[253] Especially starting from the 1990s, DRG-based payment systems have been experimented with and applied worldwide, and most European countries have developed their own systems.[254] In the Nordic countries, the NordDRG consortium is an example of a collaborative effort to develop a harmonized DRG system.[255]

DRGs have contributed to many success stories, resulting in improvements in efficiency and particularly in transparency.[256-260] The main aim of DRG-based systems is to classify the care provided to patients in clinically meaningful and economically homogeneous groups. This helps to determine the income of hospitals and allows comparisons that would not otherwise be possible.[258] This principle of paying for hospital care is often also referred to as activity-based funding, financing, or costing.[257,261-263] The payment formula is usually based on a base rate which is weighed by the cost specific for each DRG. Often, the DRGs acknowledge also the various patient characteristics such as age and sex.

However, the different DRG systems are highly heterogeneous, particularly due to the different classification variables and algorithms used, and different costing methodologies applied.[254,258,262-264] Reasons for this heterogeneity include factors such as availability of cost data on which to base the processes, input from various medical specialist associations or expert consultants, and the differing aims for group homogeneity, all these translating into differing numbers of groups.[258] In addition, parts of the process may be trade secrets.

As a result of the activity-based funding, several by-products have emerged, such as intentional upcoding and increased readmission rates.[258,265] In addition, a large study conducted within the National Health Service (NHS) in England revealed that the NHS is treating more complex patients than private providers are, which would warrant a fairer reimbursement system.[266] Many of these issues can be overcome by episode-based bundled payments, in which the cost of care is bundled throughout an episode related to the illness, a common example being a surgical procedure and the post-operative care and rehabilitation related to it. These episode-based payment

systems are increasingly applied to complement or to go beyond the DRGs; they however, share the challenges of DRGs as to the heterogeneity of grouping methodologies. Importantly, their impact on reducing costs and improving quality must be individually evaluated.[267-269] In addition, systems suitable for primary care and rehabilitation exist but they are applied on a much smaller scale.

In Finland, the current diagnosis classification system for both primary and specialty care is ICD-10. ICPC-2 (International Classification of Primary Care, Second Edition) is another diagnostic classification used in some primary care units by both nurses and doctors, but it is used to a lesser extent than is ICD-10, and it comprises a smaller number of diagnoses. All healthcare units, both inpatient and outpatient care units, must report their annual activities and patient diagnoses to the National Institute for Health and Welfare, although this is incentivized only in specialty care, which receives its income by activity-based funding. Currently, Finnish expertise on DRGs is concentrated under the Finnish Consulting Group (FCG), which manages the NordDRG system for specialty care and similar tools to use for outpatient care. The DRG-like tool applied in this thesis was developed and owned by DRG Medical Systems, until it was acquired by FCG in 2016, and harmonized with similar classification systems.

2.11 Methodological remarks on analyzing healthcare cost data

Statistical analysis of healthcare utilization data poses several challenges. The data is usually heavily skewed and contains an excess of zeros owing to the proportion of patients incurring no costs. Costs are frequently presented as both means and medians, which helps to interpret data skewness. The mean can also be used to estimate total costs to assess the total economic burden of the population. Most methods are sensitive to outliers, but no guidelines exist on how to define and handle these outliers, some of which may contain valuable information regarding the research question. When applying transformations for analytical purposes, results may be unintuitive, and retransformations can be misleading and are therefore often inadvisable. To benefit clinicians and various other stakeholders, interpretability is essential.

During the past 10 years, economic evaluations in healthcare have built on more advanced statistical foundations, often under a Bayesian framework.[270,271] However, in general, simplicity is the preference in method selection.[272] Among studies on the costs of arthritis, generalized linear models (GLMs) and ordinary least squares (OLS)

regression are common methods to control for confounding variables.[273] Patient-level cost data, however, rarely meet the assumptions of the OLS regression. Instead, using GLMs for non-normal data offers several advantages such as the ability to choose among different distribution families, depending on data and model properties. More complex methods have also been applied but are not widely recommended, as they require both substantial statistical expertise and further validation.[272] The main challenge of large registries is quality, which should be a consideration of each study in its own right.[274] Data completeness, especially, and how well it represents the population of interest deserve careful consideration.

Although DRGs and healthcare-cost data are a valuable source on their own, the utility increases considerably in combination with large-scale registries involving diverse patient-level data. Such data commonly involve laboratory measurements and comprehensive clinical information, often validated by physicians or research personnel. Leveraging these combined data requires a wide variety of clinical, statistical, and computational skills,[275] but it offers a number of potential benefits. Such benefits include assessment of healthcare delivery and outcomes, and the potential to improve identification of cost drivers.[274]

2.12 Healthcare resource utilization in rheumatic diseases

2.12.1 Understanding the therapeutic context

Not many decades ago, the long-term outlook for a majority of inflammatory rheumatic diseases was poor. Though spontaneous remission may occur particularly in early undifferentiated arthritis, a diagnosis used to indicate that at least some disability is likely to develop. Patients were commonly hospitalized with a spectrum of disease complications.

Finnish studies reached the conclusion decades ago that early and active treatment of RA is the strategy for preventing joint destruction.[21,276] This early use of csDMARDS, particularly early introduction of MTX, along with organized evaluation of outcomes were key advancements in improving the long-term outlook of RA.[277,278] Other inflammatory rheumatic diseases have achieved further gains through these strategies. This strategy of csDMARD use is still the mainstay treatment for many inflammatory rheumatic diseases, and if the response to csDRMARDs is insufficient, bDMARDs can be used.

Another wave of advancement resulted from these bDMARDs. "Beware of the biologicals—hospitals may die" states an article describing the history of the Rheumatism Foundation Hospital, Heinola, Finland (1951-2010). Progress in disease-modifying therapies had caused this hospital to face economic struggles leading to its closing.[279] bDMARDs have led to great progress in treatment of many rheumatic diseases, such as RA, PsA, AS and certain forms of JIA. [280]

2.12.2 Economic aspects of bDMARDs and tsDMARDs

The efficacy and safety of bDMARDs has been widely assessed, and evidence also for tsDMARDs is steadily accumulating. Although somewhat less popular than studies on efficacy and safety, economic evaluations of these therapies are frequently performed to justify their use. Already at their inception, bDMARDs tripled the direct costs for RA,[281] and they still constitute the largest cost component of direct costs in most rheumatic diseases. In general, changes in drug quantities and prescribed therapies, and novel drugs, are the most important determinants of pharmaceutical expenditures,[282] and there is no reason to believe this wouldn't be the case also for rheumatological care. Given the financial pressure on health systems worldwide and the influence that rheumatologists have on individual treatment decisions, understanding the economic aspects of rheumatic disease pharmacotherapy is important for all rheumatologists.

The first bDMARDs entered the market at the end of the 1990s, and they are now the fastest growing sector of therapeutics.[283] Biosimilars for bDMARDs were first introduced to the European markets a decade ago, and with accumulating evidence as to their efficacy and safety to be on par with their bio-originators,[284-286] biosimilars are increasingly prescribed and new products are licenced each year. Although the expenses for developing a biosimilar are only a fraction of those incurred in developing the bio-originator, the final price tag is affected by market competition.[287] A considerably lower price for a biosimilar is crucial to motivate its use,[287] but the wholesale acquisition cost (WAC) in some countries has been higher than forecast at entrance onto the market. For instance, filgrastim-sndz, the first biosimilar approved in the United States, had only a 15% lower WAC than did its bio-originator.[288] However, within countries with greater market competition, for instance within the EU, the estimated cost reduction is 20% to 40% lower than for the original product, which may yield considerable net savings when costs are accumulated over multiple years.[289,290] This in turn might ease the inequality in accessibility of biological therapy.

2.12.3 Cost of illness in rheumatic diseases

Even before the introduction of biosimilars, cost structures have been widely altered due to the modern treatment approaches of early and aggressive introduction of csDMARDs, and use of bDMARDs if the first-line treatment fails. Earlier, hospitalization formed the largest cost component in RA, but the rate of hospitalization has decreased[33,279] and current care is outpatient-centred. Direct costs have risen due to drug costs attributable to bDMARDs, but this is offset by a decreased incidence of work disability and lower inpatient costs.[6,281,291-293] Still, for some rheumatic diseases, the opposite trend is apparent: in gout, the hospitalization rate has doubled.[33]

Generally, high disease activity and poor physical functioning are the major determinants of cost in rheumatic diseases. This is a plausible consequence of an active disease requiring treatment efforts and more frequent follow-ups, and if inflammation persists, the resulting permanent joint damage manifests as worse physical functioning. Thereby, strategies that slow down or prevent joint destruction by minimizing disease activity are considered favorable from an economic perspective.[294,295] These aspects are evaluated both within randomized controlled trials and within real-life data, made possible by the active measuring procedures applied in standard rheumatological care.

Due to patient volume, the majority of insights on healthcare costs and cost drivers are gained from studies on RA, but at present, studies exist also on much less prevalent rheumatic diseases such as systemic lupus erythematosus[296] and giant-cell arteritis.[297] Prior studies on direct costs focus particularly on annual costs of the index disease and cost drivers. Previous sections have highlighted the similarities among the rheumatic diseases in terms of therapeutic principles and the benefits of achieving low disease activity. They have also highlighted the ways in which rheumatic diseases share follow-up and measurement strategies particularly as regards patient-reported outcomes. However, each rheumatic disease also presents unique characteristics. This thesis adopts both of these perspectives, the similarity perspective by combining the four diseases to explore shared patterns of healthcare utilization, and their uniqueness by assessing the long-term clinical and cost outcomes of JIA.

Considering that the majority of ealier studies are disease-specific, healthcare resource utilization for each disease are next reviewed in a disease-specific manner. The focus is on summarizing the key findings because detailed monetary reviews are neither particularly useful for the thesis objectives, nor easily interpretable due to study heterogeneity.

2.12.4 Healthcare resource utilization in RA

Earlier studies demonstrate the high healthcare costs associated with RA[7,298,299] The economic burden of RA is substantial,[7,8,291,300] and increased healthcare resource utilization may occur even prior to the diagnosis.[301] Studies indicate an association between increased direct costs and higher disease activity, whereas good physical function comes with lower direct costs.[294,295,302-305] Costs are shown to vary by RA treatment response and its duration.[302]

In RA, reaching lower disease activity levels has reduced both inpatient and outpatient healthcare costs and utilization.[295,305-308] In general, data from the modern era of treatments reveal an increase in medication costs, and thereby in direct costs, but this is offset by less work disability.[6,7,291,293]

Estimates of the proportion of comorbidity costs vary around 50% [303,309], and the variation likely derives from differences in study designs and in healthcare systems. Concurrent diseases may also increase hospitalization rates as evidence suggests for two important comorbidities: CVD and depression[310]. However, the impact of comorbidities on healthcare resource utilization in RA is insufficiently studied.

2.12.5 Healthcare resource utilization in JIA

Studies on the economic burden of JIA are heterogeneous and limited, particularly studies on adulthood costs. Most studies have examined mean annual direct costs in children.[311-314] Generally, costs are skewed toward patients with active disease.[315] In children, costs are increased because of pain, longer disease duration, uveitis, and with the longer delay from symptom onset to first pediatric rheumatologist visit.[314]

A study from the current treatment era in 23 patients of various ages, 10 of which were adults, reports a substantial economic burden posed by JIA with up to half the average costs resulting from non-healthcare costs and productivity losses.[316] Another study by Krause and colleagues showed increased inpatient utilization in children, but this finding did not extend into young adulthood. However, only 38 individuals were followed up into adulthood.[317] Minden and colleagues have conducted comprehensive studies on the cost of illness for both early and late JIA using German patient cohorts.[314,318] In patients followed up until early adulthood, the costs of JIA were reported to be considerable, and the costs differed among the various JIA subgroups. However, this study comprised patients referred to hospital between 1978 and 1988, which is prior to current treatment strategies.[318]

2.12.6 Healthcare resource utilization in PsA

PsA generates a high socioeconomic burden,[97,319,320] but being a somewhat rare disease, studies on its economic burden particularly in the modern era are limited. A recent large study on 35,061 PsA patients matched to controls showed that patients with PsA had both a considerably higher comorbidity burden and higher healthcare utilization than did individuals without PsA or psoriasis.[321] Cost drivers identified to date include disability, disease activity, number of comorbidities, and severity of skin symptoms.[98,322-325] Disability linked to many of its cost components and impacts the all-cause costs.[322,323,325]

2.12.7 Healthcare resource utilization in AxSpA

Most studies are conducted on AS. The largest cost component of AS is considered to be indirect costs, although estimates vary, with the highest ones reaching 80%.[326-328] In AS, longer disease duration, worse physical functioning, and high disease activity are considered important predictors of both direct costs and total costs.[129,324,327,328] Little data exists on non-radiographic AxSpA, but considering that it produces a disease burden similar to that of radiographic AxSpA, the economic burden is expected also to be rather similar.[112]

2.13 The Finnish healthcare system – a rheumatology perspective

Finland has universal public healthcare, funded mainly by taxation. The majority of the medical and much of the non-medical costs are covered by the welfare system, with a fifth of medical costs in 2014 being co-payments for health services and medications by patients.[329] These co-payments are protected by price ceilings, which, for example, regarding medications, have ranged in the 2010 decade from 572€ to 701€. Costly medications such as bDMARDs are therefore generally used when their indication exists, although the out-of-pocket costs may for some patients guide treatment strategies. Compared to many European countries, access to RA treatment in Finland is good.[330] Relevantly, the resources for treating rheumatological patients are good in the Jyväskylä Central Hospital (JCH) area.

A parallel private sector exists, covering occupational care and treating self-paying individuals along with patients holding private medical insurance, the majority of

which are accident insurance or insurance for children. Follow-up of chronic illnesses is rarely done in private clinics, particularly outside the capital area.

The healthcare system relies on strong public primary care, which also carries out follow-up of many stable chronic diseases. Many rheumatic diseases are diagnosed in specialty care, but if remission is sustained with csDMARDs, follow-up is usually transferred to primary care. In cases of symptom recurrence indicating disease activity, patients are referred back to the rheumatology clinic. Patients receiving bDMARDs are followed up in specialty care. In JCH, RA patients have follow-up visits at 3, 6, 12, and 24 months after the initial appointment. Thereafter, they are followed up in primary care with visits to the rheumatology clinic at 5 and 10 years.[29]

Each Finnish citizen has a unique personal identification number which provides the opportunity to link electronic medical records systems across different care providers and linking data from different registries.

3. AIMS OF THE STUDY

I. To explore health service-related costs and long-term outcomes in adult patients with juvenile idiopathic arthritis.

II. To compare all-cause health service-related costs of four chronic rheumatic diseases, and to investigate their high healthcare utilization.

III. To explore rheumatoid arthritis by cluster analysis to identify patient groups in need of targeted measures.

4. MATERIAL AND METHODS

4.1 Patients (Studies I-III)

The study population in this observational, registry-based study was from the Jyväskylä Central Hospital (JCH) area (population 252,000 in 2014) which has Finland's largest non-university hospital. Healthcare utilization data in 2014 was available for four municipalities in this area: Jyväskylä, Hankasalmi, Muurame, and Uurainen, comprising a population of approximately 140,000. Their primary care is delivered at the local healthcare centers, with JCH providing specialist treatment. Figure 4 and Table 7 demonstrate the patient cohorts in Studies I to III.

4.2 Clinical data (Studies I-III)

The clinical variables came from the GoTreatIT® Rheuma application (DiaGraphIt®), a structured digital database which prospectively collects data as part of the medical records. The data collection started in JCH in 2007[29,226] and we considered all data until extraction on March 16, 2016.

We identified all patients 18 or older with JIA (subtypes indistinguishable), RA, PsA, or AxSpA, diagnosed before or in 2014. Disease duration in years was counted as of diagnosis date. To capture the long-term level of the clinical and patient-reported outcome measures, we took the median of individual repeated measures. For this same purpose, instead of cross-sectional examination of medications, we defined medication use as ever- and never-users of any DMARDS, bDMARDS, MTX, or oral glucocorticoids (prednisolone and prednisone). tsDMARDs were not a part of standard care at the time of the study.

In Finland, the transition age from pediatrics to adult rheumatology is generally 16. One JIA patient had no rheumatology visits at age 18 but had visits at ages 16 and 17. This individual was excluded from Study II, but not from Study I.

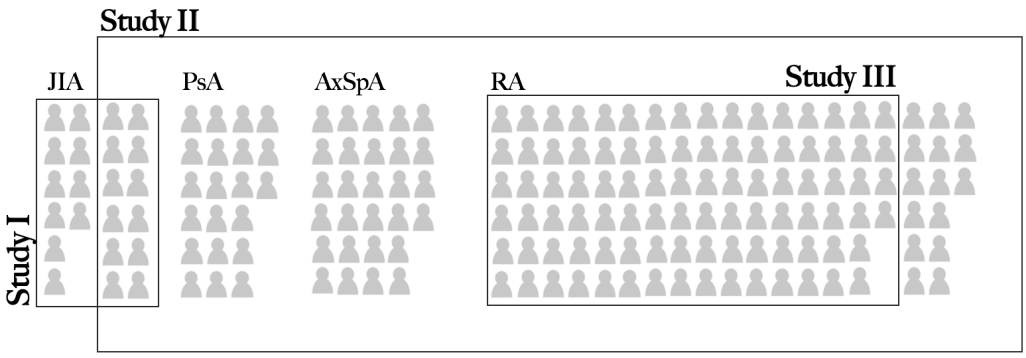


Figure 4. Patient cohorts. In Study I, for investigating clinical outcomes, we incorporated patients from the JCH area who were not in the healthcare utilization dataset, which was available for four municipalities in the central hospital area (Jyväskylä, Hankasalmi, Muurame, and Uurainen). Each silhouette represents approximately 10 individuals.

Study	Number of patients
I	Clinical outcomes of 218 JIA patients, healthcare utilization of 137 patients
II	119 patients with JIA, 213 with PsA, 1,086 with RA, and 277 with AxSpA
III	Of the 1,086 RA patients in Study II, 939 with RA who were complete cases and had rheumatology clinic visits during 2010-2014

Table 7. Number of patients in Studies I to III.

4.2.1 Disease activity (Studies I-III)

Of disease activity indices calculated by the GoTreatIt software, we used DAS28-3(ESR). DAS28-3 and DAS28-4 agree quite well at the group level, but among individual patients, the difference may be substantial due to the patients' global assessment.[162,163] We therefore chose to use the DAS28-3, in order to have a more objective disease activity measure alongside the patient-reported outcomes assessed separately. Thresholds applied for disease activity were the following: ≥3.2 for moderate or high disease activity, <3.2 for low disease activity, and <2.6 for minimal disease activity and remission, although we mainly focused on the long-term average level of disease activity. Although DAS28-3 may somewhat underestimate the disease activity of JIA, PsA and AxSpA, it was the most convenient disease activity measure for comparisons across rheumatic diseases.

Study I investigated the clinical outcomes for JIA. Patients were classified as having active disease if they had at least one contact with the rheumatology unit in 2014 with DAS28-3 ≥3.2. Patients with current active uveitis were indistinguishable from the rest.

4.2.2 Patient-reported outcomes (Studies I-III)

To assess pain and fatigue, we used the visual analogue scale (VAS; 0-100 during the past week), and for disability, the HAQ index (0-3). For HAQ disability index, 0.5 was defined as no or low disability, and values above 0.5 as moderate to severe disability.

4.2.3 Work outcomes (Study I)

We categorized employment status on the most recent visit to the rheumatology clinic as follows: 1) disabled or pensioner (combined, since some answered "pensioner", although their age indicated that they were receiving disability pensions), 2) sick leave, 3) unemployed, and 4) working or student. All causes of sick leave and disability were included, also diseases unrelated to the rheumatic disease; these were never distinguishable in our data.

4.3 Healthcare utilization data (Studies I-III)

This study falls under the category of cost-of-illness studies, assessing a specific aspect of direct costs - patient use of healthcare services. The analyses were conducted from a healthcare-sector perspective.[230] Every Finnish citizen has a unique personal identification number, which was used for combining the clinical data with healthcare utilization data. We accessed routinely recorded administrative data for the fiscal year 2014 from the electronic medical records (EMR) system. This comprises all public healthcare contacts, including contacts in both primary and specialty care, as well as contacts from outpatient care, inpatient wards, the day hospital, and the emergency department. One contact was defined as one healthcare encounter per diagnosis, such as an appointment, an inpatient episode, or tasks that include logging onto the EMR. The data covered all public healthcare contacts with all healthcare professionals: physicians, nurses, and other healthcare professionals such as rehabilitation workers.

4.3.1 Diagnosis groups

We utilized a system similar to diagnosis-related groups (DRG),[258,261,264] one suitable for both inpatient and outpatient care, to group contacts based on recorded diagnoses, either ICPC-2 or ICD-10.The grouping tool classified the ICPC-2 and ICD-10 diagnoses into 40 categories, two of which applied only in children and were not included here.

A tool developed by the former DRG Medical Systems, which is currently owned by Finnish Consulting Group Ltd, determined costs for the healthcare contacts based on disease category, age, sex, healthcare unit, and healthcare provider. These data comprised health service-related direct costs in euros rounded to the nearest integer. The data included costs of both rheumatic disease-related visits and other conditions, together referred to as all-cause costs. To avoid underestimation of costs, we also included the costs of contacts lacking ICD-10 or ICPC-2 codes. By being trained on a large body of data from both the study area and other municipalities, the grouping tool gave these contacts lacking a diagnosis code a cost similar to that for contacts with similar background characteristics. The detailed groupings and algorithms underlying the cost estimation are based on principles similar to those reviewed in section 2.10. They were not developed within this thesis and are based on trade secrets, and thus cannot not be published in this thesis. Because we assessed costs from only a single year, we applied no discount rate.

If multiple diagnoses were recorded for a visit, which is often the case, the cost was divided equally among the diseases. For nearly a decade, many Finnish municipalities, together covering the health services of over one million inhabitants, have used this tool for cost reports and process monitoring as primary goals, and for research purposes as a secondary goal. In the JCH area, many public healthcare professionals have been trained in healthcare coding.

High healthcare utilizers were identified by selecting a quantile cutpoint at which those above it accounted for a cost identical of those below it. The rest were defined as low utilizers.

4.4 Cost of bDMARDs (Study I)

For patients with JIA, to make use of all available data on this rare disease, we assessed costs of bDMARDs in 2014 from the clinical data, based on total months of use. The monthly cost was estimated at 1,000 € per patient (average retail price in 2014). The

health service-related costs included by default the intravenous bDMARDs which are administered at the hospital rheumatology clinic. The costs of csDMARDs were not retrieved.

4.5 Comorbidities

To examine the economic burden of comorbidities, we used two sources: 1) healthcare utilization data and 2) comorbidities recorded in the clinical data. The first is recorded by all healthcare professionals across the public healthcare system, and the latter is recorded into the GoTreatIt application by rheumatologists and qualified medical secretaries in the JCH rheumatology clinic. For the healthcare utilization data, we report the proportion of health service-related costs incurred by each disease category.

4.6 Ethics

In Finland, register-based studies require no informed consent from study subjects, nor ethics approval from the individual institutes. The study was approved by the medical director of JCH. Efforts to protect the patients in the registry were undertaken and we used anonymized identification numbers in the analyses. No patients were involved in planning or setting the research questions, nor when interpreting the results.

4.7 Statistical analysis

The cost data was non-normally distributed with a positive skew. For clinical data, we present the group mean of individual medians with standard deviations (SD), and for annual health service-related costs, the groups mean, median, and inter-quartile range (IQR). For both the clinical and administrative data, we report the proportion of data missing for the variables used. Due to few missing data, we performed no imputation.

For comparing two continuous variables, we used the independent t-test and in cases which violated the test assumptions, we applied the Wilcoxon rank sum test. With more than two groups, we applied the one-way ANOVA when its assumptions were met. Homogeneity of variance was assessed with Levene's test. For subsequent post-hoc testing, we used Tukey's honestly significant difference when the assumption of homogeneity of variances was met. In the skewed cost data, cost distributions of more than two groups were compared with the Kruskal-Wallis test. We compared

categorical data with the Chi-Squared test and in cases with small counts, with the Fisher's Exact Test. All comparisons were unpaired and due to planned comparisons, we did not account for multiple comparisons. All tests were two-sided.

Because patients with JIA under age 30 have likely fallen ill in the era of modern treatment strategies, we have compared those under and over 30. Costs in JIA partients with active disease were compared to costs of those with DAS28-3 <3.2, suggesting remission or low disease activity.

For assessing factors associated with annual costs, we used a generalized linear model (GLM) with a Gamma distribution and a log link function. We chose the Gamma distribution because it models non-negative data and allows for increasing variance as a function of the mean.

For those with non-zero costs in Study I, we constructed univariate GLMs for age, pain, raw HAQ, and DAS28-3. All these variables were included also in the multivariate analysis, adjusted by sex. No collinearity was detectable. Six patients whose costs exceeded the geometric mean by two SD were excluded. Often, interpretation of the magnitude of the regression effect estimates are challenging. For variables with a p-value less than 0.05 in the multivariate analysis we therefore calculated average marginal effects.[331,332] This demonstrates how the outcome - the annual costs - are influenced when the independent variable of interest increases by one unit. For testing robustness of the associations in the multivariate GLM, we also performed linear regression of inverse normal transformed costs, without outlier exclusion. A two-part model would first assess the differences between those with zero and those with non-zero costs, and then continue to analyse factors associated with costs in the latter group. Due to the low number of patients with zero costs we did not perform the first step.

Cluster analysis is an exploratory analysis method used in many fields for grouping based on similarity.[333-336] In agglomerative hierarchical clustering, all individuals start in their own group and the two groups of individuals that are the closest to each other according to the similarity measure are merged. The procedure thus generates one clustering of individuals for each possible number of clusters. The clustering variables selected were health service-related costs, median DAS28-3, median HAQ index, and median pain. We conducted an agglomerative hierarchical clustering by Ward's method.[337] After taking the square root of costs to reduce the effect of outliers and scaling the clustering variables, the similarity measure was defined by the Euclidean distance. The number of clusters chosen for a more detailed examination was based on inspection of the dendrogram. We also performed the standard principal component analysis (PCA)[338] to visualize the clusters.

When using boxplots for data visualization, the black line represents the median, the box the inter-quartile range (IQR = $Q_3 - Q_1$), the lower whisker $Q_1 - 1.5 * IQR$, and the upper whisker $Q_3 + 1.5 * IQR$. In violin plots, the white dot represents the median. Sequel Pro 1.1.2 was used to manage healthcare utilization data in a MySQL database. All other data handling and statistical analyses were carried out with R programming version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria). Conversion to marginal effects was replicated with Stata Corp version 12.1 (Stata Corp, College Station, TX, USA) since it has more methods than R for obtaining marginal effects.

5. RESULTS

5.1 Characteristics of the study population (Studies I-III)

Study I comprised 218 adult patients with JIA. Study II comprised 119 adult patients with JIA, 213 with PsA, 1,086 with RA, and 277 with AxSpA (Table 8). As of 2007 when GoTreatIt data collection began, up until data extraction in March 2016, the mean observation time for patients with JIA with healthcare-utilization data was 4.6 years (median 4.8 years, IQR 2.9-6.4), for RA a mean 5.9 years (6.5, 4.9-7.1), for PsA 5.0 years (5.4, 3.6-6.8), and for AxSpA 4.7 years (5.1, 3.0-6.5). Of these patients, only one visit to the clinic during the follow-up occurred for 10.1% of patients with JIA, for 10.8% with PsA, for 12.5% with RA, and for 18.4% with AxSpA. Of the 1,086 patients with RA, 1,013 with information on classification criteria all fulfilled the ACR/EULAR criteria. In patients with RA, RF was positive for 62.0% and ACPA for 55.6%. Of all patients with JIA, RF was positive for 6.7%.

Study III comprised 939 RA patients with no missing data, who had visits to the rheumatology clinic between 2010 and 2014. In both global and pairwise comparisons, all rheumatic disease groups differed in age ($p < 0.001$), JIA patients being the youngest with mean age 32.4, and RA patients the oldest with mean age 62.6. In addition, sex distributions differed ($p < 0.001$, global comparison).

	JIA, Study I n = 218	JIA, Study II n = 119	RA n = 1,086	PsA n = 213	AxSpA n = 277
Age	32.7 (13.8)	32.4 (13.4)	62.6 (15.0)	53.0 (14.9)	44.9 (13.7)
Female, %	73.4	77.3	71.2	43.7	39.4
Disease duration in years	24.6 (14.0)	23.3 (13.3)	14.6 (10.7)	10.9 (8.9)	13.4 (11.3)
DAS28-3	1.9 (0.8)	1.9 (0.8)	2.3 (0.8)	2.2 (0.9)	1.9 (0.8)
HAQ disability index (0-3)	0.4 (0.6)	0.4 (0.6)	0.6 (0.6)	0.6 (0.6)	0.5 (0.5)
Pain (VAS, 0-100)	22.2 (21.0)	22.6 (19.5)	29.4 (22.2)	29.6 (22.6)	30.6 (22.4)
Fatigue (VAS, 0-100)	22.9 (22.9)	24.8 (24.2)	30.8 (24.3)	28.3 (23.7)	32.3 (25.3)
Ever DMARDs, %	90.4	85.7	93.9	83.6	75.1
Ever bDMARDs, %	43.5	40.3	23.0	33.8	41.9

Table 8. Baseline characteristics (mean (SD)).

	JIA, Study I n = 218 Data Available (%)	JIA, Study II n = 119 Data available (%)	RA n = 1,086 Data available (%)	AxSpA n = 277 Data available (%)	PsA n = 213 Data available (%)
Sex	100	100	100	100	100
Age	100	100	100	100	100
BMI	98.2	99.2	96.5	97.5	99.1
DAS28-3 (ESR)	87.2	94.1	93.6	78	86.9
Pain	99.5	100	99.1	94.9	99.1
Fatigue	99.5	100	98.9	94.2	98.6
HAQ index	99.1	99.2	97.9	94.6	99.5
Disease duration	53.7	60.5	93.3	59.6	77.9
Medication data	63.3	67.2	94	75.1	83.6

Table 9. Proportions of available data. Missing data for medication is mainly explained by patients needing no anti-rheumatic medication in adulthood.

The proportion of available data in the clinical dataset are in Table 9. In the healthcare utilization data, diagnosis codes were available for 79.6% of healthcare contacts of patients with JIA, for 77.2% with PsA, for 69.8% with RA, and for 79.8% with AxSpA. For variables on contact type, unit, and profession of healthcare provider, data were available for 95.5% to 100.0%. Of the contacts lacking diagnosis code, 70.6% to 76.5% involved other than face-to-face contacts, the majority of which were non-physician contacts which have lower cost weights than do physician visits and inpatient care.

5.2 Comparison of cost distributions (Study II)

Although the diseases were heterogeneous with regard to patient characteristics, they had similar cost distributions ($p = 0.88$, Figure 5) with following annual health service-related direct costs: JIA, mean 3,631€/patient/year (median 2,164€, IQR 565-4,867€); PsA, mean 3,816€ (median 1,477€, IQR 637-4,486€); RA, mean 4,681€ (median 1,738€, IQR 707-4,922€); AxSpA, mean 3,571€ (median 1,382€, IQR 545-4,080€). Cost distributions were similar for men and women ($p = 0.33$).

Specialty care, particularly outpatient care created the largest cost component (Figure 6). Comprising the oldest patients, RA accounted for the highest relative inpatient costs (42.9%, combining primary and specialty care inpatient care). JIA and AxSpA, the diseases with the youngest average age, had the most outpatient-centred costs. Day hospital visits constituted roughly 10% of all costs, and emergency department visits for around 5%.

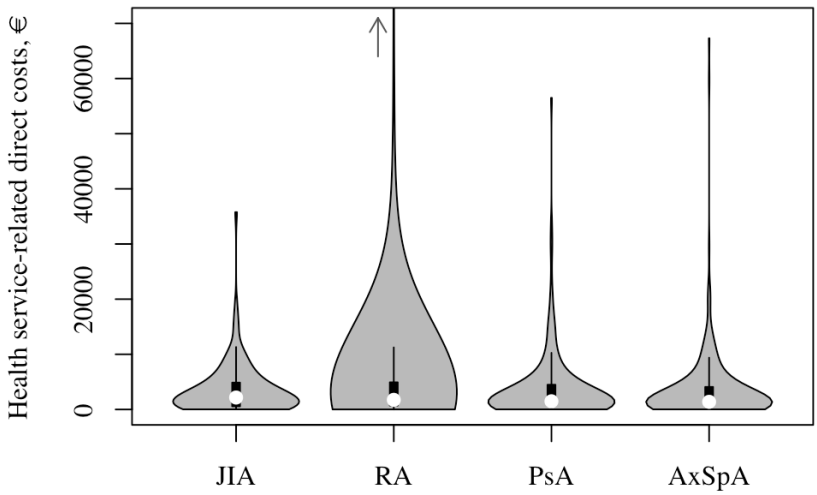


Figure 5. Boxplot on annual health service-related direct costs, on those with healthcare contacts in 2014. The cost distributions were similar (p = 0.88). Adapted from Scand J Rheumatol 2019, Mars et al., Patients with rheumatic diseases share similar patterns of healthcare resource utilization, by permission of Taylor & Francis.

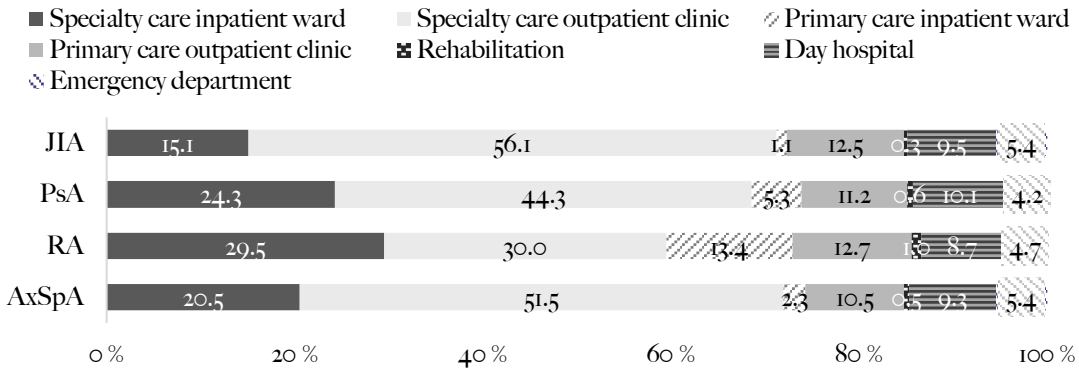


Figure 6. Proportions of costs for different healthcare units in JIA, PsA, RA, and AxSpA. Adapted from Scand J Rheumatol 2019, Mars et al., Patients with rheumatic diseases share similar patterns of healthcare resource utilization, by permission of Taylor & Francis.

5.3. Cost drivers

5.3.1 Disease activity (Study I)

A more detailed evaluation of the impact of disease activity on health service-related costs was performed for JIA. Out of the 137 patients with healthcare utilization data in 2014, 11 (8.0%, mean age 32.4 years, median age 28.7) had at least one measurement of DAS28-3 ≥3.2 and were therefore defined as having active disease during that year. Those with high disease activity had higher annual costs ($p < 0.01$; Figure 7) than those with DAS28-3 <3.2 in 2014 (mean costs 6,827€/year vs 2,835€/year, median costs 7,076€/year vs 1,311€/year). Those with active disease in 2014 showed higher levels of disability and pain, and higher usage of bDMARDs than did those in remission or with low disease activity (Table 10).

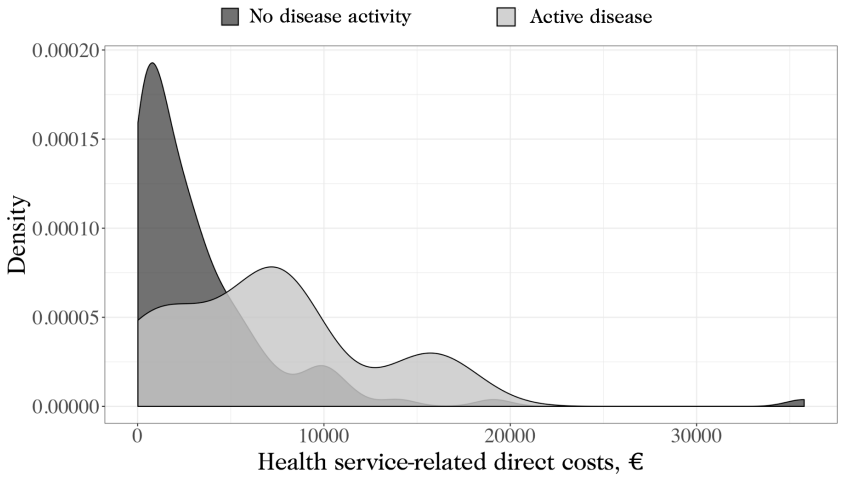


Figure 7. Density plot for health service-related costs in Study I, comparing those with active disease (defined as at least one DAS28-3 measurement ≥3.2 in 2014) to those without disease activity (DAS28-3 < 3.2 in 2014).

	At least once DAS28-3 ≥3.2	DAS28-3 <3.2
Number of patients	11 (8.0%)	126 (92.0%)
DAS28-3	3.1 ± 0.7	1.8 ± 0.7
Pain (VAS 0-100)	30.1 ± 18.0	21.7 ± 19.4
HAQ index (0-3)	0.9 ± 0.9	0.3 ± 0.5
Ever bDMARDs (%)	81.8	50.0

Table 10. Clinical characteristics for JIA patients with active disease in 2014 compared with those in remission or with low disease activity. Table modified from one published in Scand J Rheumatol 2018, Mars et al., Healthcare costs and outcomes in adult patients with juvenile idiopathic arthritis: a population-based study, by permission of Taylor & Francis.

5.3.2 Patient-reported outcomes (Study II)

To assess patterns underlying high healthcare utilization, we first defined high healthcare utilization by selecting a quantile cutpoint at which those above it accounted for a cost identical to the of those below it. In adult patients with JIA, 15% utilized as much as did the other 85%, with this ratio being 10%/90% in patients with PsA, RA, or AxSpA. High utilizers showed slightly higher levels of disease activity, although disease activity was generally low. Moreover, high healthcare utilizaters showed worse levels in many of the patient-reported outcomes: those with high utilization presented with higher average HAQ, pain, and fatigue than did the rest ($p < 0.05$ for all except pain for AxSpA and fatigue for PsA; Figure 8). However, in RA and AxSpA, high utilizers were also somewhat older ($p < 0.001$ and $p < 0.05$).

5.3.3 Comorbidity (Study II)

Comordidities incurred the largest proportion of the health service-related direct costs: in JIA, RA, PsA, and AxSpA, the index rheumatic disease comprised only 43.6%, 32.5%, 33.2%, and 31.9% (Figure 9). Compared to low utilizers, the proportional costs of comorbidities were much higher in high utilizers: in JIA, comorbidities accounted for 49.4% of the costs of low utilizers and for 63.1% of high utilizers. In PsA, these proportions were 56.8% and 76.9%, in RA 56.0% and 78.2%, and in AxSpA 57.6% and 78.5%. One-fourth of the patients had at least one healthcare contact because of infections in 2014, but their costs incurred only 1.9%–6.2%. CVDs were most common in RA, with 27.9% having at least one healthcare contact for CVDs. These CVD contacts incurred 12.8% of the annual costs in RA patients. Of patients with JIA, 13.4% had contacts for eye disorders (3.1% of costs) and in patients with AxSpA, 15.2% (2.5% of costs).

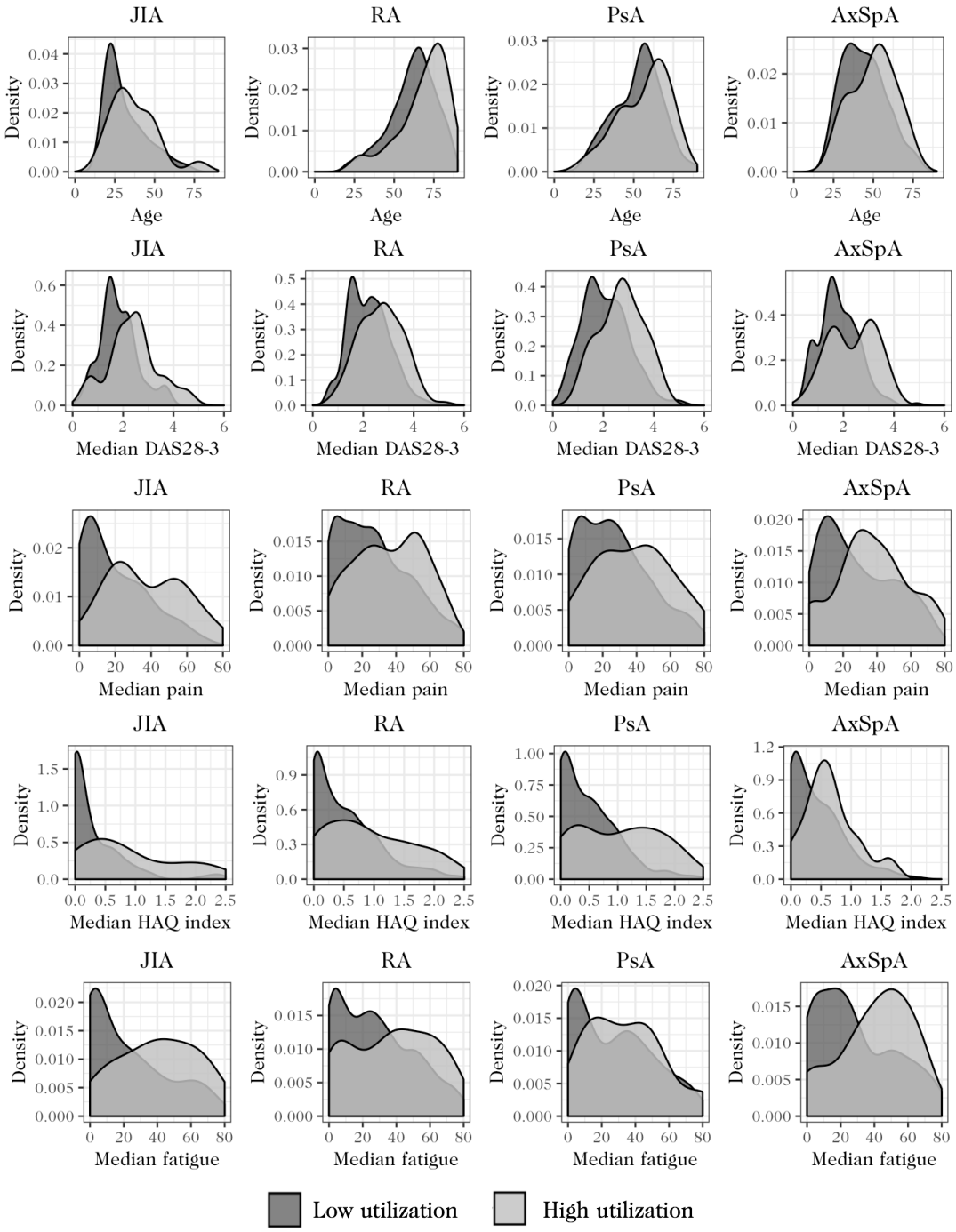


Figure 8. For high- and low-utilization groups, distributions of individual medians of clinical variables. Adapted from Scand J Rheumatol 2019, Mars et al., Patients with rheumatic diseases share similar patterns of healthcare resource utilization, by permission of Taylor & Francis.

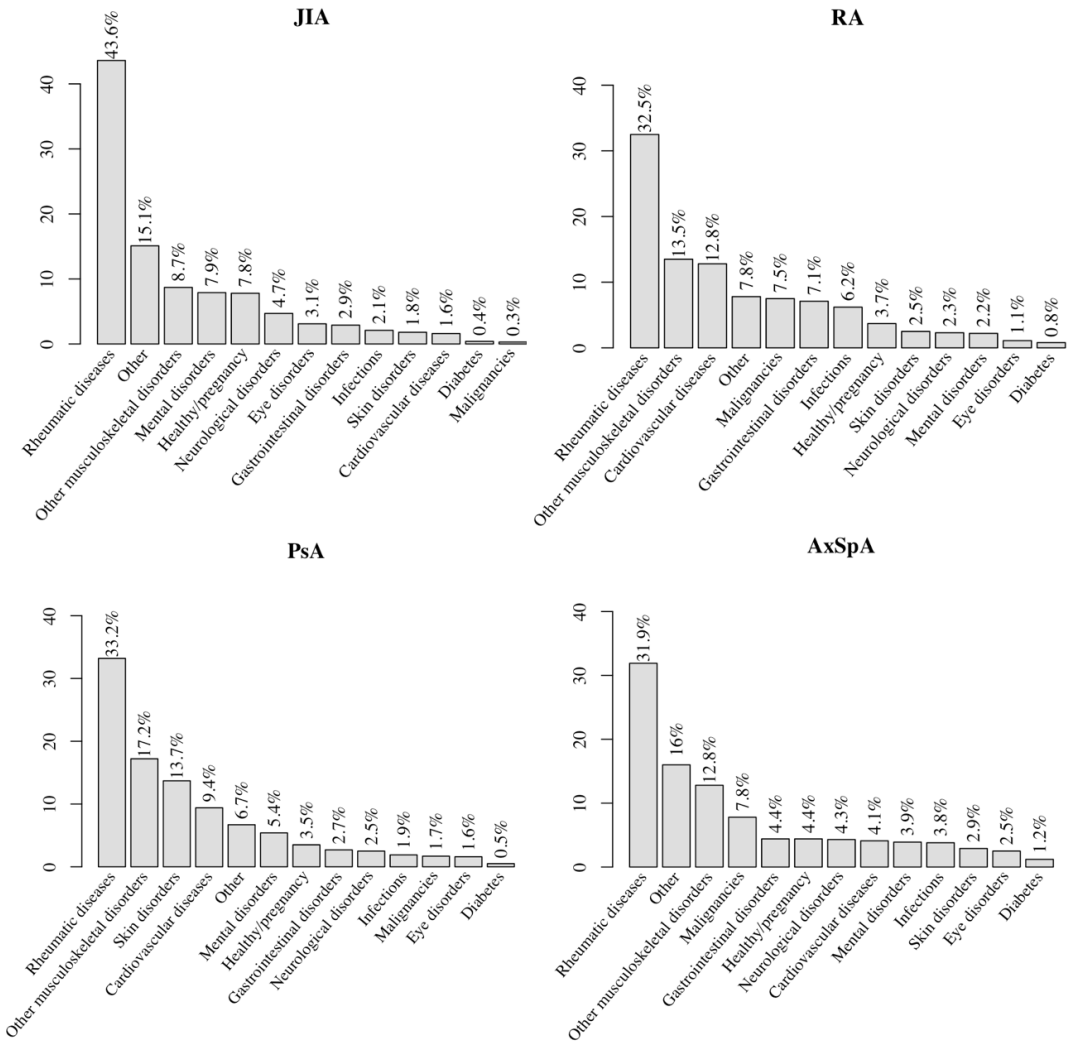


Figure 9. The proportions of annual costs incurred by rheumatic diseases and comorbidities.

5.4. Patterns of utilization in RA (Study III)

To explore whether the cost drivers incurred followed certain patterns, we used cluster analysis to study RA. The clustering variables were health service-related costs, median DAS28-3, median HAQ index, and median pain. The dendrogram illustrating cluster arrangement is in Figure 10, baseline characteristics for each cluster in Table 11, and distributions for the clustering variables within each cluster are in Figure 11.

We established four clusters, each expressing a recognizable pattern. C1 ("Remission and low costs", 550 patients, 58.6%) was the largest cluster comprising the youngest patients (mean age 58.7). Their mean costs and disease activity were low and they showed minimal disability. Their average number of comorbidities was the lowest, 2.1.

All groups showed rather high levels of pain, with the highest group mean at 53.3 in C2 ("Chronic pain, disability and fatigue", 269 patients, 28.6%). The mean being counted from individual medians indicates that many of these patients have experienced chronic pain. Other characterizing features in C2 were high average levels of disability, and fatigue. In C2, 13.4% had physician-diagnosed fibromyalgia, but in the other clusters, this was reported only in 3.6% in C1, 7.2% in C3, and 4.3% in C4.

C3 ("Inflammation," 97 patients, 10.3%) had rather high mean costs along with high disease activity. Almost half the patients were current or previous users of bDMARDs. Despite having higher disease activity than C2 ("Chronic pain, disability and fatigue"), patients in C3 ("Inflammation") had lower average levels of pain and somewhat less disability. As regards disease activity, however, all clusters were rather heterogeneous.

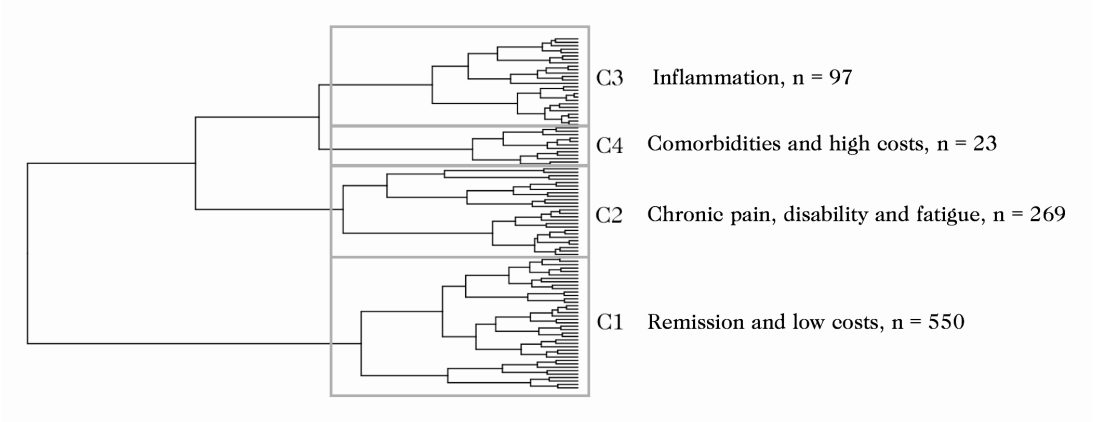


Figure 10. Cluster dendrogram - a tree graph illustrating cluster arrangement in hierarchical clustering.

	C1	C2	C3	C4
	n = 550	n = 269	n = 97	n = 23
Age, mean (SD)	58.7 (14.9)	66.6 (12.9)	66.8 (13.7)	69.2 (13.5)
Women, %	70.4	72.9	69.1	73.9
Disease duration, mean (SD)	12.2 (8.6)	16.7 (12.5)	15.8 (11.9)	15.8 (11.3)
Fatigue, mean (SD)	20.0 (18.7)	50.6 (20.6)	32.1 (19.2)	33.1 (23.7)
Ever bDMARDs. %	22.7	24.5	46.4	39.1
Number of comorbitities, mean	2.1	3.7	3.5	5.2
Mean total costs/patient, €	2,600	4,568	6,807	45,251

Table 11. Baseline characteristics of the four clusters.

C_4 ("Comorbidities and high costs") was small and heterogeneous, and all 23 patients (2.4%) had unusually high costs incurred by costly comorbidities, which encompassed mainly gastrointestinal conditions such as malignancies or bleeding, other malignancies, severe infections, and postoperative complications.

The clusters had similar proportions of erosions in hands or feet ($p = 0.24$), and similar seropositivity ($p = 0.57$). Results remained similar when repeating the analysis without costs, but incorporating costs increased the discriminative capacity (results not shown). Proportion of costs by healthcare unit are in Figure 12. In the PCA, cluster overlap was evident, and C_3 showed the most overlap with the other clusters, and C_4 was heterogeneous (Figure 13).

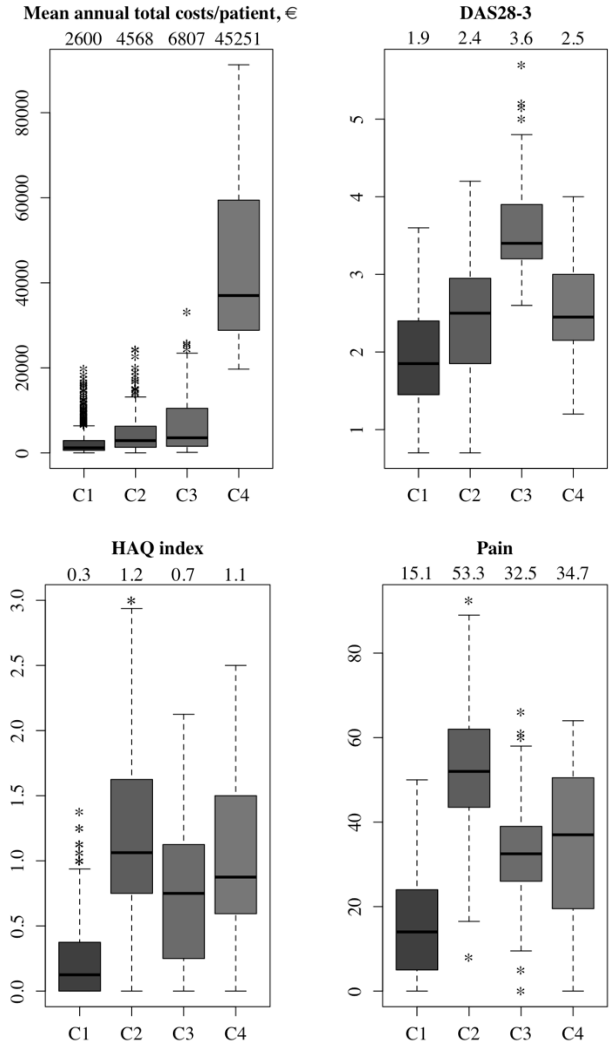


Figure 11. Boxplots of the clustering variables with group means above each plot. C_1 = "Remission and low costs", C_2 = "Chronic pain, disability, and fatigue", C_3 = "Inflammation", C_4 = "Comorbidities and high costs".

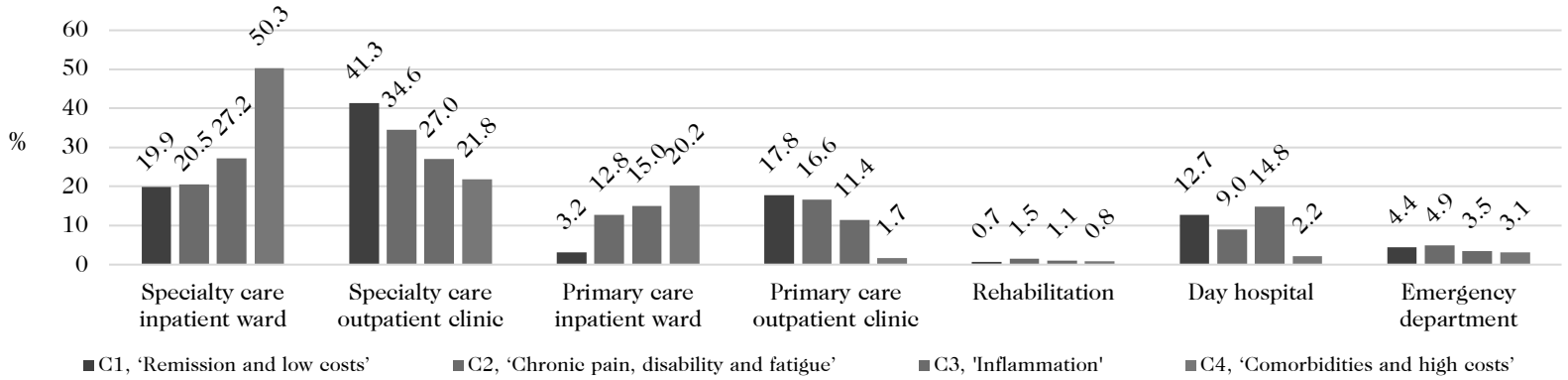


Figure 12. Proportions of costs by healthcare unit.

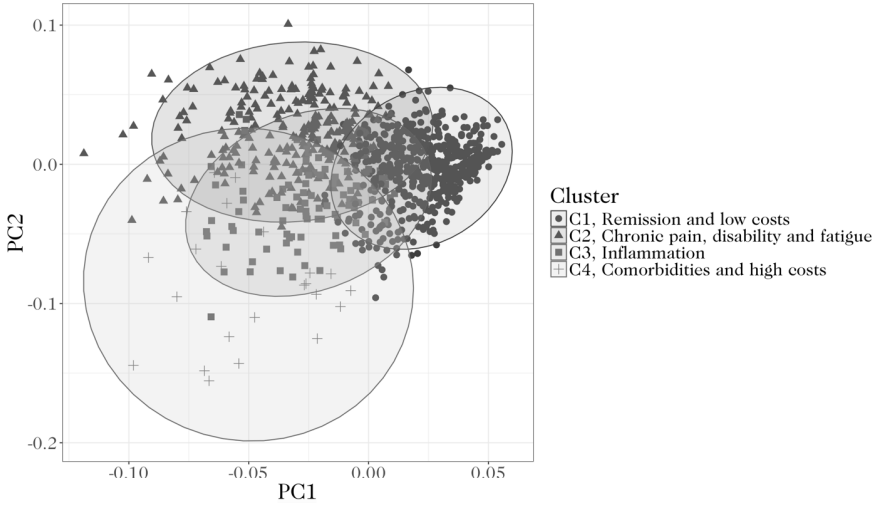


Figure 13. Plotting the second principal component (PC2) against the first principal component (PC1) indicates cluster overlap. C1 to C4 from the hierarchical cluster analysis are highlighted. These first two principal components explained 73.1% of the total variance.

5.5. Long-term outcomes in JIA (Study I)

5.5.1 Disease activity, pain, and disability

We compared adult patients under age 30 (n = 119) with those 30 and older (n = 99), as these individuals have fallen ill in eras of different treatment regimens. 90.4% were current or past users of any DMARDs, and 43.5% had received bDMARDs. Out of individuals under 30, 85.6% had a median DAS28-3 less than 2.6, while in those over 30, the proportion was 72.9% (Figure 14). Figure 15 shows density plots for HAQ, pain, and fatigue in comparisons of those under and over age 30. Individuals over 30 showed higher levels of these patient-reported outcomes ($p < 0.001$ for all). In those under age 30, 85.7% had the a rather good functional capacity (individual median HAQ less than 0.5), but this proportion was only 45.4% for those over 30. Results remained unchanged when those over age 60 were excluded (results not shown).

5.5.2 Work outcomes

Employment status on their most recent visit to the rheumatology clinic differed between the two age groups ($p < 0.001$). In those 30 years or older, 26 patients (26.3%) were retired or reported that they were entitled to part-time or full-time disability pensions. Of these 26, 20 were younger than 63 years, which is currently the youngest regular retirement age in Finland. Therefore, at least 20 patients (20.2%) among those over age 30 received disability pensions, compared to 0.8% in those under age 30. In those 30 or older, 6.1% were on sick leave on their most recent visit, whereas this proportion was only 0.8% for those under 30.

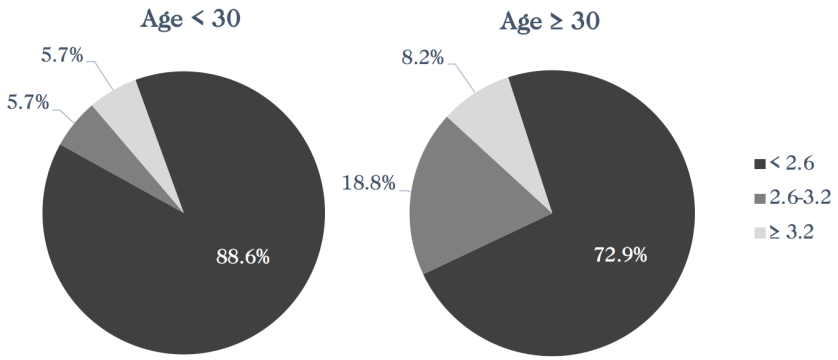


Figure 14. Adult JIA patients by different disease activity categories, <2.6 indicating minimal disase activity or remission, 2.6-3.2 low disease activity, and ≥3.2 active disease (Study I). Adapted from Scand J Rheumatol 2018, Mars et al., Healthcare costs and outcomes in adult patients with juvenile idiopathic arthritis: a population-based study, by permission of Taylor & Francis.

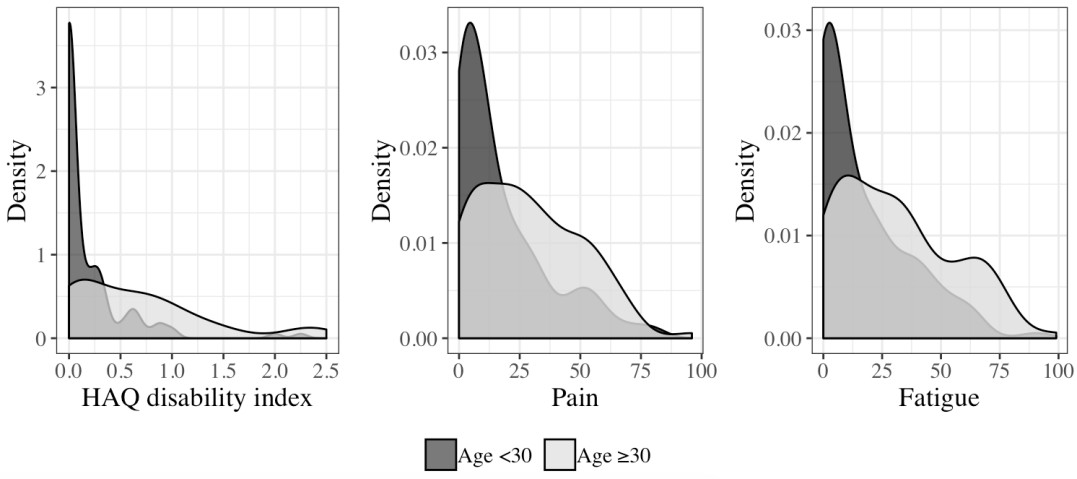


Figure 15. Distributions for HAQ, pain, and fatigue for adult patients with JIA under and over age 30.

5.5.3 Cost outcomes

In total, the annual health service-related direct costs for the 137 patients in the healthcare utilization data were 432,257€ in 2014 (mean costs=3,155€ per patient/year, median=1,569€ per patient/year). In patients under age 30 (n = 80), the annual health service-related costs were lower than those for patients older than 30 (n = 57; mean costs = 2,386€ vs 4,235€ per patient/year, median = 844€ vs 2,772€ per patient/year) ($p < 0.001$, density plot in Figure 16).

The only factor associated with costs in both the univariate and multivariate analyses was raw HAQ (beta = 0.081, p = 0.03 in the multivariate analysis, marginal effect 228€, 95% CI 3-453€; Figure 17). In separate analyses for individuals under and over 30, this association was detected only for individuals over 30 (beta = 0.066, p = 0.02 in the multivariate analysis, marginal effect 228€, 95% CI 10-446€; Figure 17).

Of these 137 patients, 36 (26.3%) used bDMARDs in 2014 for a total of 355 months (mean 9.9 months/patient), the total annual cost of bDMARDs amounting to 355,000€ (9,861€ per patient/year).

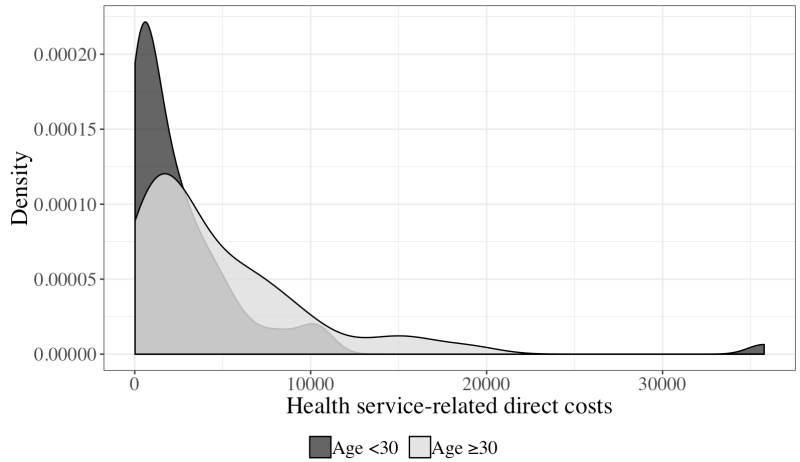


Figure 16. Density plot for health service-related costs for the adult JIA patients under and over 30 years of age.

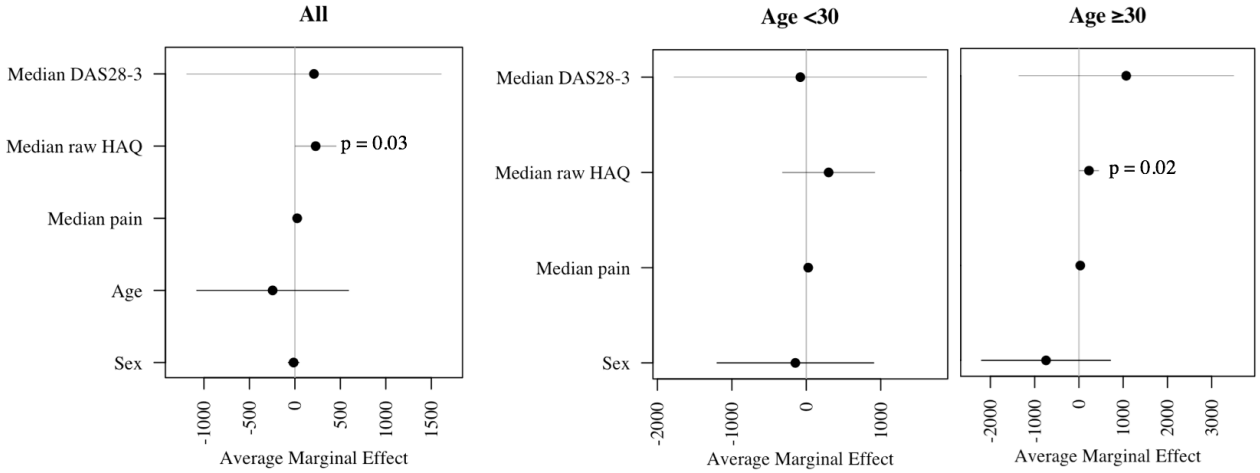


Figure 17. Factors affecting annual health service-related direct costs in adult patients with JIA.

6. DISCUSSION

6.1 Main findings

JIA, RA, PsA, and AxSpA shared similar patterns of healthcare resource utilization, both in terms of costs incurred by the rheumatic disease and by comorbidities. In these diseases, a minority can be recognized as high healthcare utilizers. These high utilizers presented with worse levels for patient-reported outcome measures, and they had a costlier comorbidity burden. Throughout Studies I to III, in addition to disease activity, patient-reported outcomes, particularly pain, but also fatigue and disability emerged as key factors affecting healthcare resource utilization. Furthermore, we provide evidence as to improved outcomes in the biologic era for adult patients with JIA.

This observational, population-based study illustrated how research on rheumatic diseases can benefit from well-recorded data on healthcare resource utilization by integrating it into clinical data on patient-reported outcome measures in a country with large-scale public healthcare. This was also leveraged with a data-driven approach in Study III, where we identified RA patient groups in need of targeted measures. The cost drivers identified in Studies I and II were evident in these clusters, merging into fairly distinct patterns. Importantly, unmet needs in terms of pain, disability, and fatigue were identified in a cluster comprising one-third of patients.

6.2 Similar cost distributions

Overall, patients with JIA, PsA, RA, and AxSpA had similar patterns of healthcare resource utilization. At a young age, adult patients with JIA and AxSpA displayed utilization patterns similar to those of much older patients with RA. This finding is important, because with disease onset occurring at earlier stages of life, JIA and AxSpA will likely lead to higher cumulative life-time costs.

Considering the heterogeneity of patients, methodology, and healthcare systems, our cost estimates of health service-related direct costs are similar to those reported by prior studies.[129,324,326,339] This heterogeneity also makes more detailed comparisons with prior studies challenging. Although some previous comparison studies have explored both the economic and disease burden, those studies took place in a different era of treatments, and none include JIA.[96,324,340,341] In these earlier comparison studies, the

overall disease burden is reported to be similar in RA, PsA, and AxSpA or AS.[3,96] In terms of costs, a review by Franke and colleagues comparing costs of RA (at mean age 57) and younger patients with AS (at mean age 47) found that RA incurred higher direct, rheumatic disease-related costs.[339] Another study by Verstappen and colleagues reached similar conclusions.[341] However, Franke and colleagues found that the relative cost distribution across different cost domains was approximately similar,[339] which was also our conclusion. Although no difference between the costs was statistically apparent, the median costs were highest in JIA, and the mean costs were highest in RA, mainly due to outliers in RA with very high costs.

That we found the diseases to have rather similar cost distributions may also result from the fact that we did not aim to compare medication costs. Given the somewhat different treatment strategies and age of onset, we would expect there to be differences for cost components such as medication costs, and work disability and the resulting indirect costs.

6.3 A minority of patients incur the majority of costs

In JIA, 15% incurred as much cost as the remaining 85%. For PsA, RA, and AxSpA, this proportion of high utilizers was 10%. A Swedish study on annual total costs of RA patients that included also costs of medication and work loss, reported this proportion to be very similar to ours, 13%.[291] Moreover, a study from the pre-biological era by Minden and colleagues found that in young adults with JIA, 12% were responsible for 55% of the total healthcare costs.[318] Similar estimates exist also for direct costs in AS.[129] Although varying definitions of cost elements, as well as different study populations and healthcare systems limit detailed comparison, these findings suggest that the pattern of high utilization is rather consistent across rheumatic diseases. Studies of the general population and of other chronic diseases imply that 5% to 10% are high utilizers.[342-345]

We were unable to assess the consistency of high utilization over a longer time period. A comprehensive Canadian study within the general population reported that the high-utilization category represented moderate stability over a three-year period. Approximately 45% of people above the 95th percentile stayed above the 90th percentile during the consecutive two years. Mortality was, however, high above the 95th percentile. Similarly, approximately 51% of those in the 90th to 94th percentile category remained at or above this level in both of the subsequent years.[346]

Between high utilizers and the rest of the patients, two differences emerged. Firstly, in high utilizers, the proportional costs of comorbidities were higher than in the rest

of the patients. Secondly, high utilizers showed slightly worse levels of disease activity and worse patient-reported outcomes.

6.4 Disease activity and costs

Despite exposing some link between disease activity and costs, many of our findings also allow us to draw some encouraging conclusions. Overall, the individual median levels of disease activity were low both in high utilizers and in the rest of the patients. In JIA, most patients had no disease activity or at most low disease activity in adulthood. In the cluster analysis of RA, two clusters, C1 and C3, implied that aggressive treatment strategies in RA have resulted in positive outcomes for the majority. C1 ("Remission and low costs", 58.6% of patients) was the largest cluster with favorable outcomes, including low disease activity, and low health service-related direct costs. C3 ("Inflammation", 10.3% of patients), although heterogeneous, had the highest individual medians of DAS28-3, but their other outcomes such as pain and disability levels were rather favourable, suggesting that although many have showed acute or chronic inflammation, effective treatment strategies have helped to maintain many patients' physical functioning. These findings are in line with ones discovered earlier of a generally improved outlook for many patients with rheumatic diseases in the era of modern treatment strategies.[15,347,348]

We performed a more detailed analysis of the impact of disease activity on costs for JIA patients in Study I. Patients with active disease, defined as at least one DAS28-3 measurement ≥3.2 in 2014, had annual health service-related direct costs over twice as high as those of patients with no or low disease activity. In children with JIA, costs are generally skewed toward patients with active disease.[315] With a median age of 28.7, our JIA patients with active disease were rather young. To better understand this pattern of high disease activity in conjunction with high health service-related costs in JIA, larger studies are warranted. Assessing the impact of important treatment challenges, such as poor adherence to treatment[349] can be recommended for future studies.

6.5 Impact of patient-reported outcome measures on costs

In all the studies, patient-reported outcomes, particularly pain but also disability, were important factors affecting healthcare resource utilization. As mentioned earlier, high utilizers with JIA, RA, PsA, or AxSpA showed worse levels of patient-reported outcomes, with the largest differences emerged for pain, but also for disability and fatigue. Although being conducted over a decade ago, a Swedish study by Hallert and

colleagues reached similar conclusions, with high utilizers with RA having higher HAQ and higher levels of pain.[350]

In Study III, characterizing features of cluster C2, which comprised one-third of the RA patients, were chronic pain, disability, and fatigue. However, only half of them showed moderate or higher disease activity, and fibromyalgia was diagnosed in 13.4%, indicating that much of their symptoms were not explicitly linked to disease activity; instead, many of these patients seemed to have chronic, multifactorial pain.

Pain, fatigue, and an impairment in quality of life are often reported residual symptoms in RA.[351] Fatigue is associated with various features of rheumatic diseases: disease activity, disability, and the comorbidity burden.[51] Fatigue is also often linked to chronic pain. When Lee and colleagues explored subgroups of RA patients to examine pain, fatigue, inflammation, and psychosocial factors, they reached similar conclusions with subgroups similar to our clusters C1, C2, and C3. Patients who showed high levels of pain presented with minimal inflammation but with symptoms indicative of chronic widespread pain syndrome.[352]

In rheumatic diseases, both pain and fatigue in are multifactorial.[148,353] Pain can result from active inflammation which may lead to irreversible joint destruction, but pain-regulation mechanisms may also be altered.[148] In the general population, pain is likewise an important factor affecting healthcare expenditures.[354,355] Depression in RA patients is associated with increased levels of patient-perceived global disease activity and pain.[356] Depression is also a common comorbidity in other patients with pain[357] and some have found it to be highly prevalent in high healthcare utilizers.[358]

Recent reviews and guidelines identify pain and physical functioning as important areas of unmet needs in RA.[359,360] Regardless of its aetiology, pain both acute and chronic should receive active treatment in rheumatic diseases, both by both lowering disease activity, and by treating the pain itself by with both pharmacological and non-pharmacological treatment, such as exercise therapy or sometimes by means of orthopaedic surgery. Patients with chronic pain might also benefit from the support of a multiprofessional team.

A link between disability and costs was apparent in all of our studies, a finding supported by numerous earlier investigations.[129,305,322-324,327] Despite our small sample size for JIA, disability measured by HAQ was associated with costs. HAQ is affected by multiple factors such as age and other sociodemografic factors. [196,217] Our HAQ variable comprised individual medians, reflecting the average level of disability over the whole follow-up. In early RA, HAQ increases, and it tends to decrease when the

initial acute inflammation is treated, increasing again if chronic impairment and joint damage occur.[361]

6.6 Comorbidities – a substantial cost component

We can draw two important conclusions from our results on comorbidity. Firstly, the health service-related costs of comorbidites between the rheumatic diseases were fairly similar. Although overlooked by many studies, the finding that a majority of costs in rheumatic diseases may be incurred by comorbidities is supported by earlier research.[303] Overall, for RA, PsA, and AxSpA, only about one-third of costs (for JIA, 43.6%) were incurred by rheumatic diseases; comorbidities caused two thirds of the costs. To our knowledge, this is the first study in adult JIA patients to describe the comorbidity burden as to both the detailed comorbidity prevalence and the resulting direct healthcare resource utilization, and to assess them alongside figures for other rheumatic diseases. Furthermore, for RA, PsA, and AxSpA, few have assessed comorbidity-related costs this widely, and few studies have included comorbidities that are not directly linked to the index rheumatic disease.[97,303,362]

Our second, albeit a more careful conclusion is that higher rheumatic disease activity may have contributed to a greater and costlier comorbidity burden. Looking at high utilizers only, the proportion of comorbidity costs was higher than when looking at all patients; the proportion of rheumatic disease costs was only one-fourth (a third for JIA) of the total costs for RA, PsA, or AxSpA. Given that high utilizers comprised a higher proportion of bDMARD ever-users and had slightly higher levels of DAS28-3, they may have had a history of more inflammation. Due to the small absolute number of high utilizers, we were unable to assess this finding further.

In Study III, the most distinct feature of the smallest cluster, C4, was that these patients had severe and costly comorbidities, in particular, consisting of severe infections, cancer, and severe gastrointestinal disorders, all of which may potentially be linked RA. These patients also had a rather high average level of DAS28-3, and 40% were previous or current users of bDMARDs.

An association between disease activity and cardiovascular diseases is well recognized.[49,363] Crepaldi and colleagues examined the relationship between RA disease activity and comorbidities, concluding that among the many comorbidities assessed, disease activity was influenced by cardiometabolic comorbidities, in particular diabetes, ischaemic heart disease, and obesity.[364]

6.7 Identifying patterns of utilization in RA

Although over half the patients did generally well with their disease and had low costs, we also identified patients with unmet needs in terms of pain, fatigue, disability, and comorbidities. Our analysis demonstrated a data-driven approach to identify patients with RA in need of targeted measures. Cluster analysis captures information beyond that identified by traditional research methods, and has verified clinically relevant clusters in many medical specialties[365,366]; studies in clinical rheumatology have applied cluster analysis for ANCA-associated vasculitis [367] and gout.[368] Some studies have undertaken efforts to subgroup arthritis patients based on patient-reported outcomes,[352,369] but to our knowledge, no studies have included costs when clustering RA patients.

Despite identifying rather distinct clusters, these were still fairly heterogeneous. Finding more homogeneous clusters would require selecting a much smaller number of clusters. Cluster analysis is also sensitive to the selected clustering variables, and differing sets of variables highlight different aspects, likely bringing out somewhat different subgroups. Studying the indirect costs within these clusters would provide additional insights and we speculate that indirect costs would be high particularly for cluster C2 ("Chronic pain, disability, and fatigue").

6.8 Long-term outcomes in JIA

The aim of treatment of JIA in both children and adults is no disease activity and full functional capacity. Timely introduction of MTX and bDMARDs has led to great progress JIA treatment.[370] Still, many patients fail to achieve remission, either in childhood or later in adulthood. Studies estimate that approximately half continue to show disease activity in long-term follow-up, but many of these patients had fallen ill in a different era of treatments.[69-71]

Differences in healthcare systems, and heterogeneous study populations and cohorts, particularly regarding disease subtypes, limit comparability of our findings with those of earlier studies.[69,72,318,371,372] Our estimate of patients with active disease was much lower than were previous estimates,[70-72] at only 8%, and most patients with JIA had low or no disease activity in adulthood. This lower estimate may be affected especially by two factors. Firstly and importantly, our data represent a modern population-based JIA cohort in which many patients had received modern treatment regimens, which is likely to have influenced their outcomes. Secondly, our estimate is, however, also likely to be an underestimation of disease activity, because our definition of disease activity

was limited to one year and we were unable to reliably identify individuals with active extra-articular manifestations such as active uveitis. Despite ours being a population-based dataset, some patients with favourable outcomes in early childhood may not have been included.

Our aim was to assess the long-term outcomes of JIA in adulthood, and the impact effective treatment strategies have had on this patient group, by comparison of patients under and over age 30, that is, before and after advances occurred in treatment strategies. Patients younger than 30 showed lower costs, lower levels of disease activity, and considerably more favourable patient-reported outcomes than did patients older than 30. In those under 30, disability was rare, but in those over 30, disability pension was common and present for one-fourth, despite their rather low mean age of 44.6. In these older patients, the individual median HAQ level exceeded 0.5 in 54.6% and on these patients' most recent visit to the rheumatology clinic, HAQ was 0 in only 40.4%. A long history of JIA before modern treatment strategies and availability of bDMARDs may have permanently damaged their joints, manifesting as worse physical functioning leading to higher healthcare resource utilization. Fortunately, modern treatment regimens make it unlikely that the younger patient group will have to face the outcomes of the older group. Although our findings suggest a decreased disease burden resulting from modern active treatment strategies, the aim of no disease activity and full functional capacity is still to be met.

6.9 Strengths

This study linked two population-based datasets: a clinical dataset with longitudinal follow-up and high diagnostic validity, and healthcare utilization data covering all public healthcare visits in a country with universal public healthcare.

Studies are frequently unclear as to whether they have looked at only index disease-related costs at all-cause costs. Healthcare resource utilization is often evaluated with questionnaires, some of which have extrapolated 3-month utilization to a year.[295,327,341,350,373] One study on AS reported that patients appear to overestimate their healthcare visits in comparison to routine general-practice and hospital administrative records.[327] Our utilization data represent true utilization recorded by healthcare professionals both in primary and specialty care, and it includes not only healthcare contacts for rheumatic diseases, but also for other diseases. The specialty care costs represent the true societal payments. Patients in long-term remission are in Finland followed up annually in primary care, and even if the only contact were laboratory monitoring for DMARDs, that patient would still be included in the utilization data.

The patients were diagnosed, treated, and followed up in a rheumatology clinic. Changes in rheumatologic diagnoses are registered, which reduces the risk for misclassification. Comorbidities in the clinical data are verified by rheumatologists and the clinical measures are widely used in clinical practice. Both datasets were collected as part of routine practice by healthcare professionals, and the extent of missingness in key variables was low.

6.10 Limitations

This study has some important limitations. Heterogeneity of populations and healthcare systems limit comparability to prior studies. The impact of potential coding errors and misclassification in the healthcare utilization data, a limitation shared with other administrative data,[274] is reduced by use of larger disease categories instead of detailed diagnosis codes. The private sector in the region studied treats mainly private insurance-holders and occupational-care patients, and so the costs are minor compared to those in public healthcare. We expect this mainly to lead to underestimation of our comorbidity costs.

Our aim was to assess only health service-related direct costs. We did not aim to compare indirect costs nor costs of medications and did not retrieve that sort of data. Costs of bDMARDs administered in the day hospital were under the day-hospital costs, and bDMARDs are likely to constitute the largest cost component.[374] Indirect costs and costs of medications are important components of the economic burden, and it is likely that differences between rheumatic diseases would arise if these were compared. However, the largest differences in medication costs would arise primarily from differences in bDMARD use.

The number of JIA patients with active disease was too low for more detailed analyses and we decided to leave out detailed cross-sectional individual data, such as current medications of those with active disease, and focus on group-level differences. Investigating indirect costs in JIA would require a larger number of patients, perhaps as a collaboration with multiple clinics or with addition of nationwide data. A larger study would also allow assessment of patterns for work disability in the younger patients, since disability pensions and sick leaves in our JIA patients under age 30 were almost non-existent. Moreover, the spectrum of reasons for disability pensions is expected to be large.

Although many clinical trials have used DAS28 to evaluate disease activity in PsA, it is formally validated only for RA.[159] It is not validated for adult patients with JIA, nor is it the primary choice for AxSpA. For these diseases, DAS28 may underestimate

disease activity, mainly due to not capturing the spectrum of symptoms involved in the disease.[168,375] However, DAS28 is widely applied to measure disease activity index in adult rheumatology clinics, where adult JIA patients receive treatment. Based on our clinical experience, patients who are intensively followed up in our rheumatology clinic in adulthood have symptoms of juvenile polyarthritis or extended oligoarthritis, supporting the applicability of DAS28. A study by Miyamae and colleagues also applied DAS28 when investigating long-term outcomes of JIA in adult Japanese patients, 93% of whom had poly- or oligoarthritis.[372]

JIA subtypes were instinguishable in our data. Bertilsson and colleagues found that after 17 years of follow-up, the subtype at onset had changed in up to 44%.[66] Therefore, after a patient's transition to adult rheumatology clinics, the disease subtype may not always be distinguishable, particularly a few decades after disease onset, which was the case in our registry-based study. Many were diagnosed in the Rheumatism Foundation Hospital (1951-2010), which no longer exists, hindering access to information recorded at disease onset.

Because disease activity is an important cost driver in other inflammatory rheumatic diseases, this was an important area to study in JIA. Using this narrower definition of disease activity allowed us to explore the economic burden of this rare disease in the modern era of treatment. In the multivariate regression analyses, disease activity was not associated with annual health service-related direct costs, but our study may also be underpowered to detect such associations.

6.11 Impact and generalizability

Firstly, the major findings of our study relate to the impact of patient-reported outcomes, particularly pain, on healthcare resource utilization. Secondly, we expanded previous observations that comorbidity is an important cost driver in rheumatic diseases. Thirdly, this study also achieved one of its main objectives, which was to report and explore patterns of healthcare utilization of patients of a Finnish rheumatology clinic with highly elaborate care chains. We also illustrated how research on rheumatic diseases can benefit from well-recorded data on healthcare resource utilization by integrating it into clinical data on patient-reported outcome measures in a country with large-scale public healthcare.

Being conducted in a population-based setting, this study provided results that are representative of the Finnish population and can be generalized to similar healthcare- and social-security systems, particularly in Nordic countries. Finland has large-scale

public healthcare, which is mainly tax-funded. Applying these results to insurance-based healthcare systems would require more confidence in labelling and careful consideration of the ethical aspects, since clustering could essentially be used to pigeonhole patients into various health plan categories. However, the healthcare needs that this thesis highlights are likely to be relevant also outside the Nordic coutries.

6.12 Future research

Along with complementary data on indirect costs and costs of medications, the findings of this study need to be repeated in larger datasets with longer follow-up. The ever-growing databases can be useful in further assessing these associations by combinining clinical and administrative datasets with large-scale biological information, such as genomic data. Particularly for JIA, leveraging information on disease subtypes is important in the future. Further comparison studies are needed involving a wider spectrum of diseases such as systemic lupus erythematosus.

The indirect costs are of particular interest in individuals with poor patient-reported outcomes, who comprised one-third of the RA patients. Moreover, the cluster analysis could be performed for all rheumatic diseases simultaneously, or for individual rheumatic diseases beyond RA, if data is available for a sufficient number of patients. As research applying cluster analysis is, above all, hypothesis-generating, this might reveal further interesting patterns for advanced analyses performed in more traditional research frameworks. Analyses in the large databases may also highlight more detailed disease patterns accountable for both favourable and unfavourable outcomes.

7. CONCLUSIONS

I: Modern treatment regimens have entailed good long-term outcomes for the majority of JIA patients, although room still exists for improvement in terms of reducing disease activity and disability.

II: Patients with JIA, RA, PsA, and AxSpA shared similar patterns of healthcare resource utilization, both in terms of costs incurred by the rheumatic disease and by comorbidities. Of the health service-related direct costs, two-thirds were comorbidity costs. Approximately one-tenth of these individuals can be classified as high healthcare utilizers. Patient-reported outcomes, particularly pain, were important cost drivers.

III: A large proportion of RA patients are doing well and have low healthcare resource utilization. Unmet needs identified in one-third of patients were pain, disability, and fatigue.

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